Case Report

Pulmonary Langerhans Cell Histiocytosis: Can it Originate from Chest Trauma?

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Abstract

Langerhans cell histiocytosis (LCH) is a rare medical condition which is defined by abnormal accumulation of a heterogeneous population of Langerhans cells that form nodules in certain tissues such as the skin, bone, and lungs. When the lungs are involved, the disease is called pulmonary LCH (PLCH). It is well established that PLCH is frequently observed in young adult smokers with equal gender distribution. Despite the clear role of smoking in PLCH pathogenesis, being a smoker rarely induces the disease, suggesting that host-related factors, inhaled antigens, or other stress-related factors may contribute to the pathogenesis. Here, we reported two cases of PLCH which both presented after chest trauma. Based on the findings from both the cases, it is concluded that the overstimulated inflammatory response in the posttraumatic lungs might be the responsible etiology resulting in the LCH if the lungs are already damaged and more sensitive due to smoking. We suggest that the differential diagnosis of PLCH should be especially considered in young adults with sudden or insidious onset of symptoms following chest trauma.

Keywords: Interstitial lung disease, Langerhans cell histiocytosis, pulmonary, trauma

Introduction

Langerhans cell histiocytosis (LCH) is a rare medical condition which is defined by abnormal proliferation and accumulation of a heterogeneous population of Langerhans cells (LC), a type of dendritic cell (DC), along with other different acute and chronic inflammatory cells forming nodules in certain tissues such as the skin, bone, and lungs.[1,2] LCH can present as a single-system disease with unifocal or multifocal involvement, as a multisystem disease, or as a mixture of multi-system disease with a single risk-organ involvement such as the bone marrow, liver, spleen, or central nervous system.[3] Multisystem lesions tend to be seen in children with different syndrome variants such as Letterer–Siwe disease, Hand–Schuller–Christian Syndrome, histiocytosis X, or Hashimoto–Pritzker Syndrome.[3]

When the lungs are involved, the disease is called pulmonary LCH (PLCH). PLCH is a relatively rare interstitial lung disease with nodular inflammatory lesions in small airways seen in mostly young adult smokers with equal gender distribution.[4] It is seen as a localized or a multisystemic disease of the lung with the localized subtype being seen more prevalently and was previously named eosinophilic granuloma.[5] The localized form of the disease tends to have a more indolent course with the potential of spontaneous recovery. Based on

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the latest studies, PLHC was responsible for 3%–5% of all diffuse pulmonary diseases of adults.[4] However, it is assumed to be a misdiagnosed or an underdiagnosed disease in several cases; therefore, its incidence and prevalence are not well established.[4]

Clinical presentation of PLCH varies from asymptomatic to rapidly progressive disease with the common symptoms of cough, chest pain, progressive dyspnea, weight loss, and fever. Spontaneous pneumothorax was also observed in 25% of patients during its course.[1,6] The radiographic characteristics of PLCH comprise a combination of cavitary nodular opacities and cystic lesions of the middle and upper zone of lungs.[3] Although analysis of bronchoalveolar lavage or lung biopsy might be required for definitive diagnosis, most cases are diagnosed with suspicion raised from the clinical presentation and characteristic imaging findings of the patient.[1] Therefore, the key in the establishment of the diagnosis of PLCH is the high degree of clinical suspicion.

The main mechanism that is responsible for the pathophysiology is the clonal accumulation of a large number of CD1a+ cells in the form of granulomas due to increased levels of certain inflammatory cytokines and chemokines. Although the exact mechanism is unclear, smoking also contributes to the pathophysiology by causing epithelial injury and promoting the secretion of these chemokines and growth factors. Despite the obvious role of smoking in PLCH pathogenesis, being a smoker rarely induces the disease, suggesting that host-related factors, inhaled antigens, or other stress-related factors may contribute to the pathogenesis.[2,4] Therefore, discovering the mechanisms by which LC initiates and enhances airway immune responses is essential to understand the pathogenesis of LCH. Here, we reported two cases of PLCH which both appeared after chest trauma, and our aim is to investigate the possible relationship between chest trauma and PLCH.

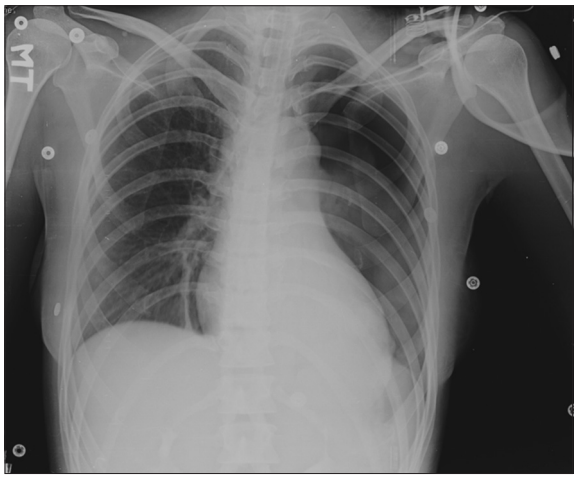

Figure 1: Chest X-ray of case 1. Her chest X-ray was showing bilateral nodular opacities with possible lesions in the upper and middle zones of both lungs

Case Report

Case 1

A 31-year-old woman was admitted to the emergency department with trauma to her head and chest after a traffic accident. The mechanism of her injury was described as blunt head and chest trauma. In her initial assessment, she was unconscious with normal vital signs. She had a history of smoking with no dyspnea, chest pain, or other complaints prior to the traffic accident. She has no previous history of diabetes mellitus, hypertension, or ischemic heart disease. Her liver and renal function tests were normal, and her values of complete blood count were also within normal limits. Her cardiac exam and echocardiography did not show any abnormal findings. Her chest X-ray was showing nodular opacities with possible lesions in the upper and middle zones bilaterally [Figure 1]. The computed tomography (CT) scan of her head confirmed the head trauma, and she was taken directly to the operating room for decompression surgery [Figure 2]. After the surgery, the extracted bone of the skull was sent to the pathology department for further analysis.

Following the surgery, she was complaining of progressive dyspnea and her chest high-resolution CT (HRCT) was showing bilateral diffuse cysts with pulmonary nodules, especially in upper and middle zones which were consistent with LCH [Figure 3]. Her pulmonary function test also showed mild obstruction. Her bone biopsy result was showing infiltration of LCH with eosinophils, neutrophils, lymphocytes, and plasma cells. Otherwise, there were no abnormal findings or complaints regarding involvement of any other organ system. Since her radiologic and clinical findings were compatible with those seen in PLCH, the diagnosis of PLCH with bone infiltration was made. Therefore, she was prescribed corticosteroids and recommended with smoking cessation. She was followed up regularly every 3 months for 2 years for possible recurrence and assessment of progression. Her condition improved and she had been stable ever since.

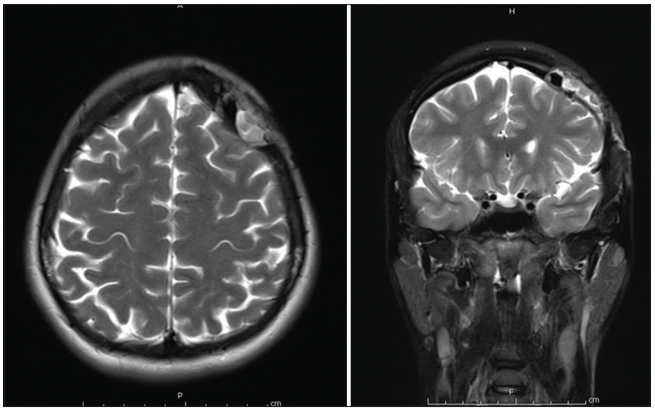

Figure 2: Head computed tomography of case 1. Her head computed tomography after traffic accident showing the decompressed part of the head prior to surgery

Case 2

A 25-year-old man has consulted an outpatient clinic with unproductive cough and progressive dyspnea on exertion for 3 years. He is a heavy smoker with a history of 20 packets/year smoking. His medical history has no previous illnesses or other complaints. His personal history includes a bomb explosion in a military vehicle 3 years ago and his dyspnea started and has worsened since then. His chest X-ray showed bilateral diffuse opacities, especially in the upper and middle zones of the lungs [Figure 4]. In his HRCT of the thorax, bilateral multiple diffuse solid nodular cysts and cavities in small airways were observed [Figures 5 and 6]. There were no abnormal findings or complaints regarding any other organ system. His pulmonary function test revealed a mild obstruction. PLCH diagnosis was made based on his smoking history, possible damage from inhaled substances in the bomb explosion and most importantly based on his characteristic radiological findings. He was prescribed corticosteroids and recommended smoking cessation. He has been followed up regularly every 3 months for 2 years and his condition showed improvement since then.

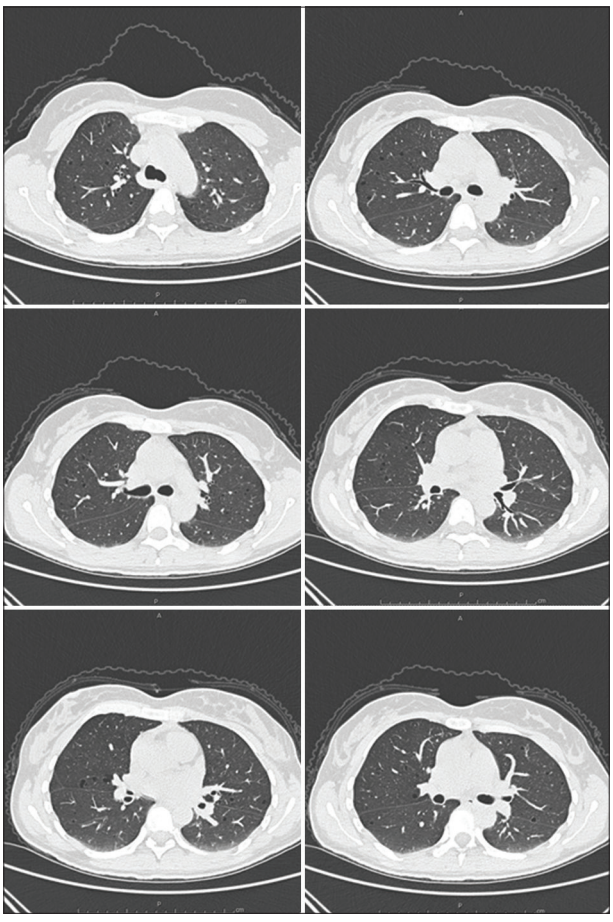

Figure 3: Thorax high-resolution computed tomography of case 1. Her chest high-resolution computed tomography scan was showing bilateral diffuse cysts with pulmonary nodules especially in upper and middle zones which was consistent with Langerhans cell Histiocytosis

Discussion

Despite being a rare interstitial lung disease of adults, the lung is the most commonly affected organ in adult LCH.[1] In its early stages, the predominant pathology is the inflammatory and destructive bronchiolitis and interstitial inflammation with loosely formed granuloma-like nodules which are distributed around small airways. In addition to bronchiolar and interstitial inflammation, varying degrees of vasculopathy and irregular parenchymal cystic lesions are also observed frequently.[1,2,4] Therefore, the histologic differential diagnosis includes other smoking-related diffuse lung diseases such as respiratory bronchiolitis, desquamative interstitial pneumonia, and eosinophilic pneumonia. On the other hand, the radiologic differential diagnosis includes other interstitial diseases of the lungs with cystic and cavitary nodules.[4] It is also possible that these diseases proceed to PLCH as Donohue and Quill indicated.[7] The correct diagnosis can be made by matching the common clinical presentations (such as nonproductive cough, dyspnea, chest pain, spontaneous pneumothorax, and constitutional symptoms such as fatigue, weight loss, and fever) with characteristic radiological findings (reticular or nodular cystic opacities with cavities). Clinical examination and routine laboratory tests in PLCH are usually unremarkable.[3]

While its pathophysiology remains unclear, DC colonization in the lungs by the activation of mitogen-activated protein kinases (MAPK) and nuclear factor κ B (NF-κ) pathways via increased production of tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), and transforming growth Factor alpha (TGF)-beta that happens in response to smoking or other predisposing factors is thought to be the main mechanism responsible for PLCH.[2,4] It is known that immature DCs reside in alveolar epithelium, alveolar septae, and around pulmonary vessels in healthy lungs. Discovering the mechanism of action by which specific LCs

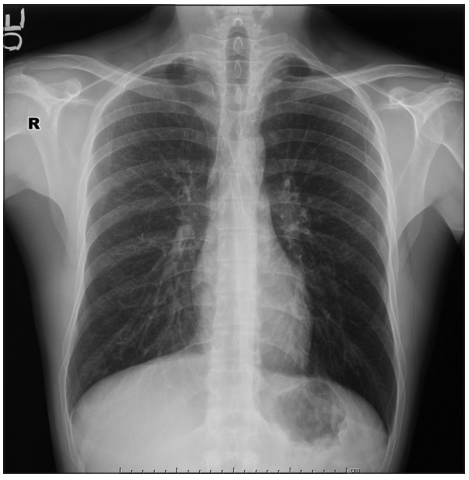

Figure 4: Chest X-ray of case 2. His radiography was showing ill-defined nodules with reticonodular changes predominating at the upper-middle lobes

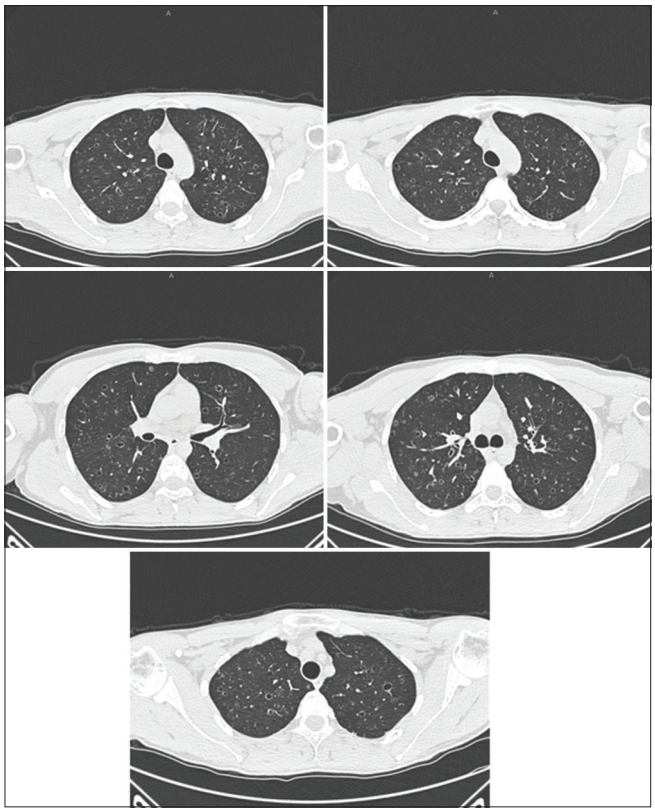

Figure 5: Thorax high-resolution computed tomography of case 2. The axial cross-sections were demonstrating bilateral multiple diffuse solid nodular cysts and cavities in small airways

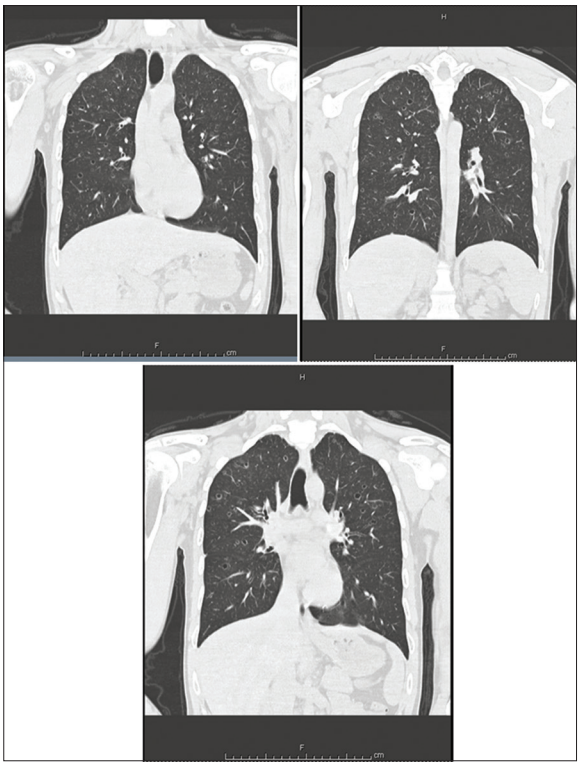

Figure 6: Thorax high-resolution computed tomography of case 2. The coronal cross-sections were showing typical distribution of disease with many diffuse cysts and cavities localized in upper and middle lung lobes, with some micronodules. As expected, basal regions were spared

provoke the inflammatory process is fundamental to have in-depth knowledge about the disease.[2] It is thought that the accumulation of CD1a+ cells results from differentiation of resident and peripheral blood myeloid hematopoietic precursor cells in the tissues involved with the help of GM-CSF, CCL20, and CCL2. Furthermore, neoangiogenesis, cell signaling, and cell adhesion molecules are also involved for the recruitment of other inflammatory cells along with LC.[2] Moreover, the presence of activating BRAF (V600E) mutations has also been blamed to be responsible for pathogenesis by inducing the oncogenic activation of MAPK signaling pathway.[3]

Specifically, the pathologic LCs reported having a different phenotype and altered function compared to their physiologic ones. In other words, these pathologic LCs that cause PLCH respond in an exaggerated way to exposure to pathogens or activating cytokines, compared to their normal phenotype, which together stimulates the Notch1 signaling pathway.[2] This different phenotype, together with T-lymphocytes, is blamed to be responsible for tissue destruction. On the other hand, smoking induces the accumulation of CD1a+ cells via increased local production of cytokines, matrix metalloproteinases, glycoprotein osteopontin, antiapoptotic molecules in LC, and possibly increased stimulation of the MAPK pathway.[4] It is also demonstrated that excessive recruitment of circulating monocytes (potentially directly induced by smoking) is likely to be an essential mechanism for the expansion of DC and LC around small airways.[4] Although much is known about the retention and activation of DCs and LCs, the real mechanism by which those inflammatory nodules promote small airway remodeling and destruction remain incompletely characterized. It is also still unclear whether this mechanism is driven by local proliferation of the cells residing in the lungs, which may provide evidence to the clonal nature of the disease, or recruitment of those cells from peripheral blood. Based on the current knowledge, it can be hypothesized that smoking-induced PLCH is a distinct type of histiocytosis in the sense of having more reactive rather than a clonal proliferative process.[4]

Blunt chest trauma is a frequent injury that often leads to lung contusions that precipitates severe local and systemic alterations. It has been shown in several studies that alveolar macrophages seem to produce an increased number of chemokines (MCP-1, CCR2) in response to blunt trauma which induces the differentiation of resident DC and migration of mononuclear cells and myeloid precursors from peripheral blood.[8] While the differentiation of monocytes into DC s and further recruitment of macrophages contribute to recovery from trauma, in some cases, they sustain the posttraumatic inflammatory state and lead to further pathological complications such as acute lung injury or acute respiratory distress syndrome (8–10).[9] A DNA microarray study following blunt chest trauma has revealed an increased expression of

inflammatory and coagulation proteins as well as complement factors (such as TNF-α receptor, IL-1α, IL-1 β, C3a, NF-κB, and plasminogen activator).[10] Venet *et al*. also demonstrated that plasmacytoid DCs control the lung inflammation and monocyte recruitment following lung injury.[11] Since the pathological consequences of overstimulated immunological responses are still unclear, the possible basis of inflammation in PLCH should be further investigated.

It is known that PLCH has a yet unknown but polyetiological mechanism which cannot only be triggered by local damage such as blunt chest trauma but also induced by predisposing factors such as smoking or genetic factors. Ehrnthaller *et al*. indicated that particularly for lung injury inflicted by blasts (e.g., in the military settings), as in our case 2, the underlying pathophysiology of the inflammatory response and its possible complications is still poorly understood.[10] Perl *et al*. indicated that early cytokine increment following blunt chest trauma, as in our case 1, may be a possible mechanism for acute pulmonary complications since it is also accompanied by a simultaneously impaired pulmonary endothelial barrier.[8]

Based on the presented cases, we hypothesized that possible inflammatory over response might provoke LCH in the lungs of young smoker adults. It seemed that although no symptoms existed prior to trauma in both cases, smoking has already provided a basis for possible injury in the lungs. Therefore, it is concluded that the overstimulated inflammatory response in the posttraumatic lungs might be the responsible etiology resulting in the LCH if the lungs are already damaged and more sensitive due to smoking. However, some limitations of the study include the lack of previous chest CT images of patients and the lack of knowledge about the exact timing of the initiation of this disease. Based on the reported findings, further laboratory studies are fundamental to demonstrate such a relationship. This report can be a starting point to retrospectively investigate more patients to see whether an altered lung microenvironment gave rise to the same condition. It should be kept in mind that most PLHC diagnoses are missed or delayed; therefore, more knowledge and detailed studies will be essential to lower the number of such missed cases.

Conclusion

PLCH is a rare disease of young smoker adults, and the diagnosis of a PLCH case is often missed or delayed. We suggest that PLCH should be among the differential diagnosis, especially in young adults with smoking or inhalation of substance history and patients with a typical radiological presentation of cystic and cavitary lung disease. Based on the findings of our report, it is suggested that the diagnosis of PLCH should be especially considered in young adults with sudden or insidious onset of symptoms following chest trauma.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Author contributions statement

All the authors have read the manuscript and contributed equally to the manuscript writing process. D. E. and S. O. have evaluated the clinical aspect of patients and generate the hypothesis, while E. A. and I. K. have had a significant role in the literature search and manuscript writing processes.

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Conflicts of interest

There are no conflicts of interest.

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