Case Report

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Early and Atypical Radiologic Presentations of Pulmonary Langerhans Cell Histiocytosis: A Report of Two Cases

폐 랑게르한스 조직구 증식증의 비전형적 영상 소견: 2예에 대한 보고

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Pulmonary Langerhans cell histiocytosis (PLCH) is a rare, multi-systemic disease primarily affecting young male adults with a history of smoking. The two patients with PLCH in our report showed relatively early and atypical radiologic presentations at initial evaluation. On chest CT, PLCH presents variable radiologic features depending on the evolutional stage of the disease. Atypical CT features of PLCH may render precise radiologic diagnosis difficult and usually require lung biopsy for a confirmation of the diagnosis. Our case review is aimed at raising the awareness of radiologists on the atypical CT features of PLCH, to help make accurate radiologic diagnosis and prevent unnecessary and invasive diagnostic procedures.

Index terms Histiocytosis, Langerhans-Cell; Lung; Tomography, X-Ray Computed; Radiography

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a proliferative disease characterized by monoclonal proliferation and infiltration of organs with Langerhans cells (1). Lung involvement may occur either in isolation or as part of a multi-organ disease.

Chest CT is a useful and sensitive tool in the diagnosis of pulmonary LCH (PLCH). The combination of diffuse lung cysts with irregular outline and small peribronchiolar nodules, sparing the lung bases is a characteristic radiologic presentation of PLCH, which may allow the clinician to make a diagnosis without a lung biopsy. However, PLCH can show atypical radiologic features at initial presentation that can lead to delayed diagno-

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sis or misdiagnosis. In this case report, we describe two patients of PLCH with early and atypical radiologic presentations requiring differential diagnosis with other important lung diseases including malignancy.

CASE REPORTS

CASE 1

A 50-year-old male was admitted to our hospital due to cough and sputum for a month. He had a medical history of diabetes mellitus and was a heavy current smoker (30 pack-years). He had no history of dust or chemical exposures and was previously healthy. His vital signs were blood pressure 101/61 mm Hg, pulse 82/minute, respiration rate 20/minute, and body temperature 37.2°C. Auscultation of the chest revealed mild wheezing sound and pulmonary function tests revealed mild obstructive pattern with normal diffusion capacity for carbon monoxide. All laboratory findings were within normal limits.

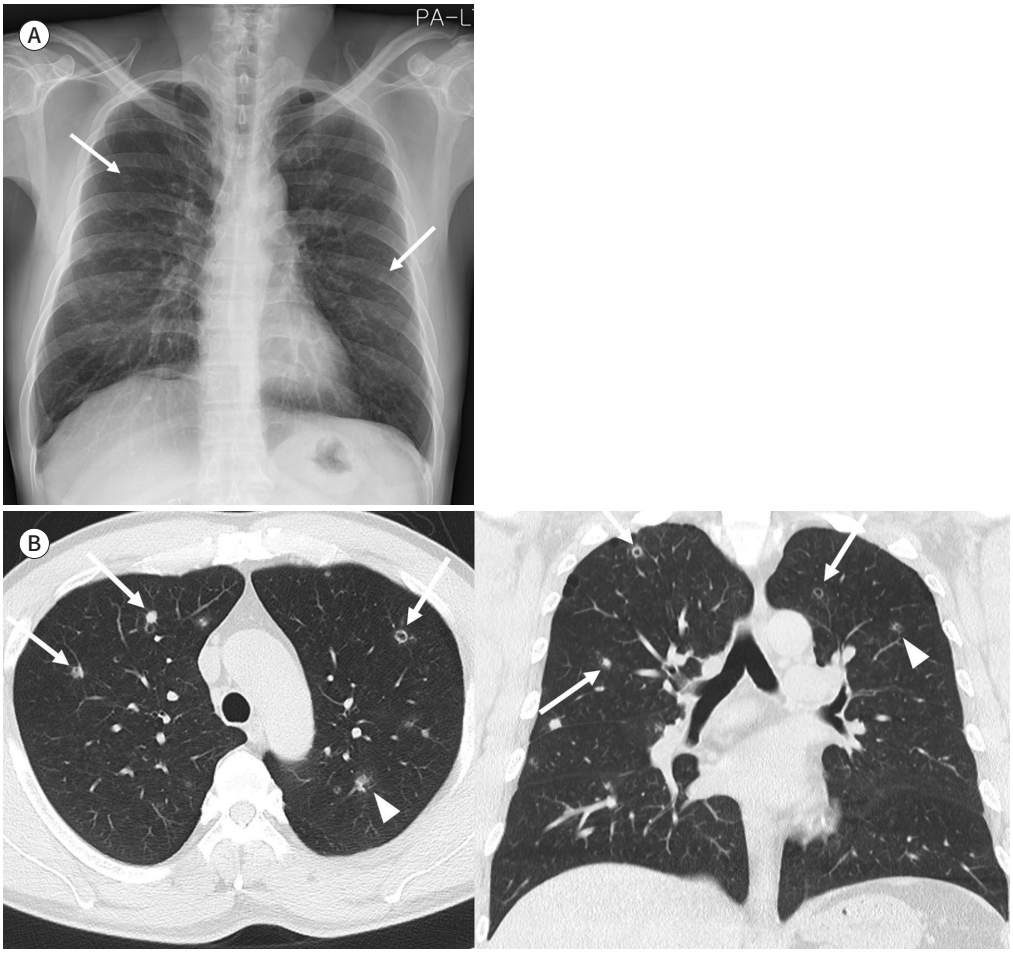
Chest radiography showed newly appeared multiple nodular opacities in both lungs with relatively upper lung predominance, as compared with the last exam before 6 months (Fig. 1A). Subsequent chest CT revealed mild distal acinar emphysema in both upper lobes and diffuse bronchial wall thickening. Multiple cavitary and non-cavitary nodules were seen with peribronchiolar distribution and also craniocaudal predilection in upper lungs. The nodules measured less than 10 mm in diameter and some of them showed peripheral ground-glass opacity (GGO) (Fig. 1B). The radiologic differential diagnoses included hematogenous lung metastasis from unknown primary malignancy, fungal infection, and tracheobronchial papillomatosis. Two days later, ^{18}F-fluorodeoxyglucose (FDG) PET/CT scan was performed for systemic evaluation of malignancy. Increased FDG uptakes were noted in the most of pulmonary nodules (Fig. 1C), however, no evidence of primary malignancy was identified. We performed a video-assisted thoracoscopic surgery (VATS) with a lung biopsy of nodules in left upper lobe. Histologically, the lesion showed a stellate nodular infiltrate extending into alveolar septal interstitium. The cellular infiltrate consisted of Langerhans cells and many eosinophils. On immunohistochemical stain, Langerhans cells showed diffuse and strong positivity for S-100 protein and CD1a expression (Fig. 1D, E). On clinical review, there was no evidence of other systemic involvement and PLCH was diagnosed. Smoking cessation was strongly recommended to the patient and follow-up CT after 3 months revealed partial improvement with decreased size of lung nodules (not shown).

CASE 2

A 44-year-old male was hospitalized in our hospital due to dyspnea, cough and chest discomfort for a week. He had no specific medical history and was a heavy current smoker (30 pack-years). His vital signs were blood pressure 140/95 mm Hg, pulse 72/minute, respiration rate 20/minute, and body temperature 36.3°C. The physical examination was not remarkable. Pulmonary function tests were not performed and all laboratory findings were within normal limits.

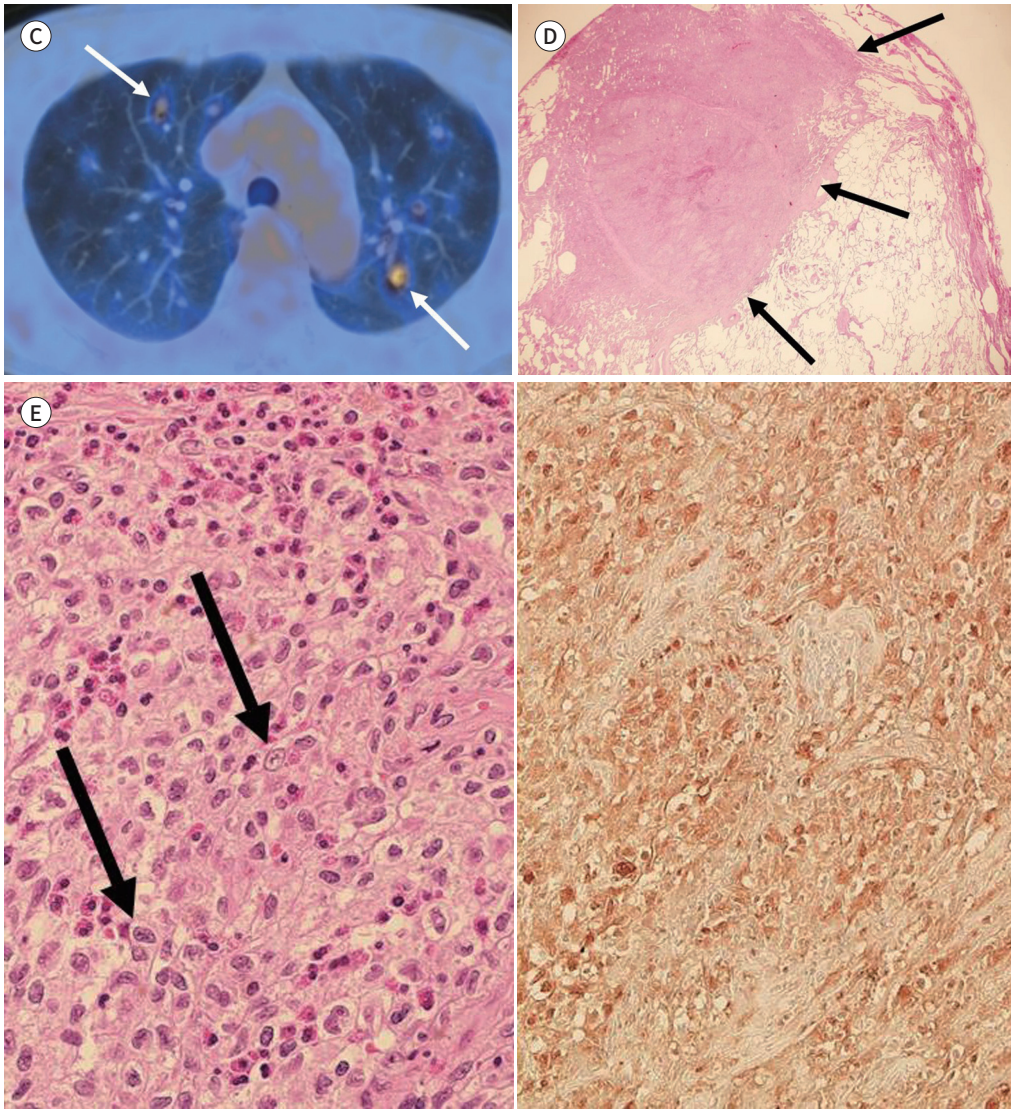
Initial chest CT showed small amount of right pneumothorax and uniform round, thin-walled and variable sized multiple cysts in both lungs. The lung cysts revealed no remarkable

Fig. 1. A 50-year-old male with pulmonary Langerhans cell histiocytosis.
A. Chest radiography shows *de novo* multiple nodules in both lungs, relatively sparing the lung bases and costophrenic recesses (arrows).
B. Six months previously, there was no remarkable abnormality in the parenchyma of both lungs on CT (not shown). Follow-up chest CT during hospitalization shows *de novo* multiple cavitary and non-cavitary nodules with peribronchiolar distribution (arrows). Some of nodules reveal peripheral ground-glass opacity (arrowheads).



zonal predilection and also involved bilateral costophrenic recesses. Lung parenchymal nodules and any other abnormality were not identified (Fig. 2A, B). The primary radiologic diagnosis was pulmonary lymphangioleiomyomatosis (LAM). Due to the male gender of our patient, our differential diagnoses also included Birt-Hogg-Dubé syndrome (BHD), lymphocytic interstitial pneumonia (LIP) and PLCH. An open lung biopsy by VATS was performed in right middle lobe and right lower lobe. Histologically, the lung lesion showed multiple nodular cellular infiltrate with marked cavitation. The cellular infiltrate consisted of a few Langerhans cells and eosinophils (Fig. 2C). On immunohistochemical stain, Langerhans cells showed weak S-100 protein positivity and negative expression for human melanoma black-45 (HMB45) (Fig. 2D). The patient did not receive any treatment and his subjective symptoms were improved during the follow-up period for a month after discharge.

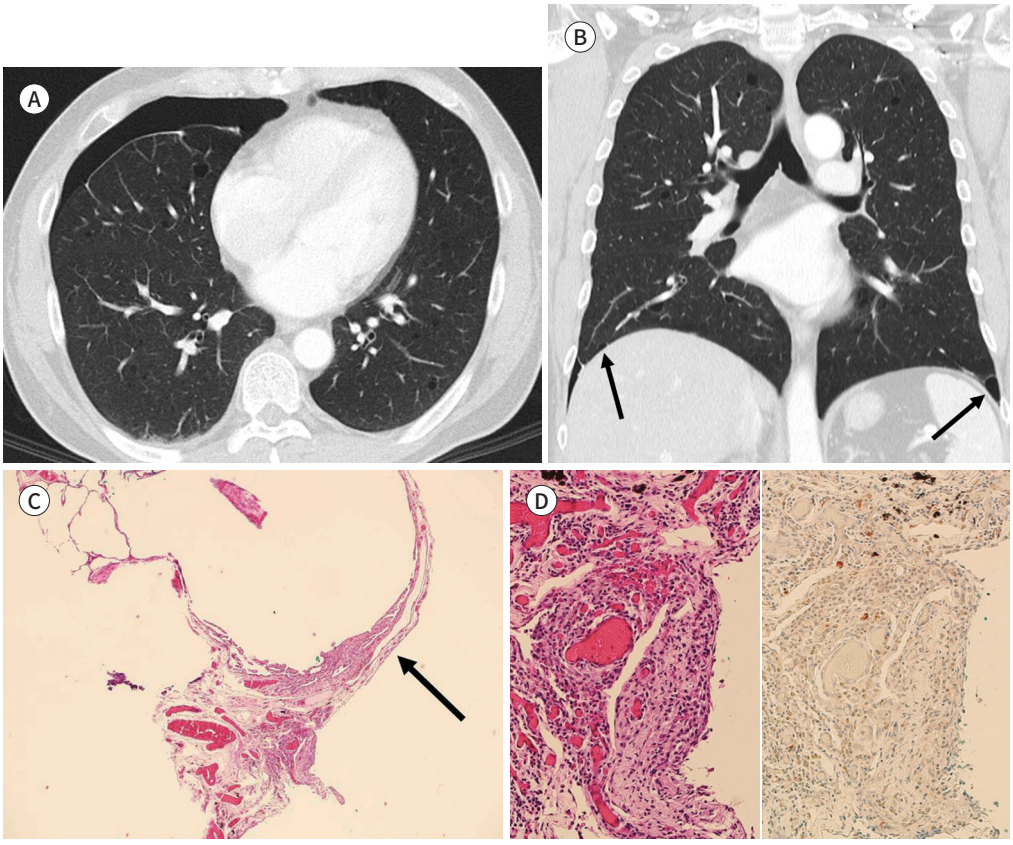
Fig. 1. A 50-year-old male with pulmonary Langerhans cell histiocytosis.
C. ^{18}F-FDG PET/CT, axial fusion image shows increased FDG uptake in most of the pulmonary nodules (arrows).
D. On microscopy, the lung specimen shows a stellate nodular infiltrate extending into the alveolar septal interstitium (arrows) (hematoxylin and eosin stain, × 40).
E. The cellular infiltrate consists of Langerhans cells and many eosinophils. On immunohistochemical stain, Langerhans cells show diffuse and strong S-100 and CD1a expression (arrows) (× 200, hematoxylin and eosin stain and S-100).
FDG = fluorodeoxyglucose



DISCUSSION

PLCH is an idiopathic disease histopathologically characterized by abnormal proliferation of Langerhans cells and cyst formation, with associated involvement of the interstitium and pulmonary vasculature. The disease shows characteristic peribronchiolar accumulation of Langerhans and other immune cells that form stellate nodules. With progression, cellular nodules can cavitate and precede the development of airway remodeling with bronchiolar

Fig. 2. A 44-year-old male with pulmonary Langerhans cell histiocytosis.
A. Initial chest CT scan reveals uniform round, thin-walled and variable sized multiple cysts in both lungs. There is also a visible small amount of right pneumothorax.
B. A coronal reformatted image shows multiple cysts with no zonal predilection, involving bilateral costophrenic recesses (arrows).
C. On microscopy, there is a markedly cavitating lesion (arrow) with a few cellular infiltrations on lower power field (hematoxylin and eosin stain, × 40).
D. The cellular infiltrate consists of a few Langerhans cells and eosinophils. On immunohistochemical staining, Langerhans cells show weak S-100 protein positivity (× 200, hematoxylin and eosin stain and S-100).



destruction and eventual formation of lung cysts. In later burnt-out phase, fibrotic scars are surrounded by enlarged and distorted air spaces (1). The etiology of LCH remains obscure, but the vast majorities (approximately 90%) of the patients are current smokers or ex-smokers of less than 40 years of age or have a history of exposure to substantial second-hand smoke (1-3). Males tend to develop symptoms at earlier age than females. The prognosis is variable, ranging from spontaneous remission to progressive disease and death. Common symptoms are cough, dyspnea and occasionally chest pain (2).

Chest CT has been known to help diagnosis and assessment of histopathologic activity of PLCH (3). The characteristic CT findings include the combination of multiple, irregular bizarre shaped cysts with small peribronchiolar distributed nodules, predominant in upper and mid lungs. However, the radiologic appearances of PLCH depend on the disease phase with evolution of CT findings over time (1). The early "florid granuloma" is characterized by cellular peribronchiolar nodules possibly surrounded by GGO secondary to inflammatory in-

terstitial infiltration (1, 4). When inflammatory activity is decreased, many nodules can present cavitation and become predominantly cysts. Cysts may appear round and small dimensions (< 1 cm), but in later phase, they become typically larger and of different shapes. Irregular, bi-lobed, cloverleaf, branched or bizarre shaped cysts are derived from further cystic dilatation and fusion of adjacent cysts. End-stage disease is characterized by a fibrocystic pattern that maintains zonal predominance in upper and mid lungs (4). Because PLCH can exhibit all evolutionary stages, it can show many faces on initial radiologic evaluation.

One of our patients revealed only a limited number of non-cavitary and small cavitary nodules, which were newly developed on follow-up CT in less than a year (6 months). With the noncharacteristic CT features, a variety of diseases from benign inflammation to malignancy should be considered. Nevertheless, prominence in the upper lungs and identification of nodules with lucent center or peripheral GGO in a patient with heavy smoking history can raise the diagnostic possibility of PLCH. Nodules with peripheral GGO correspond to the early "florid" phase, which can be interpreted as active inflammation and have potential for regression (3). In our patient, follow-up CT demonstrated spontaneous well regression of pulmonary nodules after smoking cessation during the follow-up period of 3 months (not shown). We assume that this case may represent a very early reversible stage with limited presentation of PLCH. In our knowledge, initial presentation of PLCH like our case has been rarely reported and many diseases can be included in the radiologic differential diagnosis, which include miliary infection, sarcoidosis, amyloidosis, pneumoconiosis, tracheobronchial papillomatosis, rheumatoid lung nodules, septic embolism, and malignancy. And it is particularly important to exclude malignancy, that is, hematogenous lung metastasis (5). Many cases eventually need to be confirmed by lung biopsy; nevertheless, radiologists should be well aware of early and very limited initial presentation of PLCH and which can be included in CT differential diagnosis, particularly in a heavy smoker. Furthermore, unnecessary and invasive diagnostic work-ups can be avoided in some of the patients; if a clinico-radiologic diagnosis of PLCH might be strongly suspected, close follow-up evaluation with smoking cessation can lead to confirm spontaneous regression of disease.

In case 2, our patient showed multiple uniform thin-walled cysts in both lungs with no significant zonal predominance and also involving bilateral costophrenic recesses. The radiologic differential diagnosis of diffuse cystic lung disease includes LAM, BHD, LIP, centrilobular emphysema, bullae, cystic bronchiectasis, pneumatoceles, honeycombing and cystic metastasis. Among these, LAM and PLCH can be primary radiologic differential diagnosis of diffuse thin-walled cysts and it is important to know their distinguishing features (6). LAM occurs almost exclusively in women of childbearing age, which is characterized by smooth muscle cell proliferation of the lung parenchyma, airways, lymphatics, and blood vessels, associated with areas of cystic change. On chest CT scan, LAM shows diffuse thin-walled cysts which are typically round or ovoid, uniform, usually 2–10 mm in diameter and surrounded by normal lung without zonal sparing. Associated abnormalities include pneumothorax, renal angiomyolipoma, chylothorax, chylous ascites and abdominopelvic lymphangioleiomyomas (6, 7). In contrast to LAM, PLCH is smoking-related lung disease, with 80–100% of cases seen in patients who have smoking history. On chest CT scan, cysts in PLCH are irregular and thick- or thin-walled, later becoming bizarre in shape and vary in number and size. Also,

they show predominance in upper lung zones, having a tendency to spare costophrenic recesses and multiple lung parenchymal nodules are more frequently accompanied in PLCH (8). BHD is a rare autosomal-dominant disorder characterized by hair follicle tumors (skin fibrofolliculomas), pulmonary cysts and renal neoplasm. Multiple thin-walled lung cysts with variable size and shape are predominantly seen in lower, peripheral lung zones and paraseptal location, surrounded by normal lungs on chest CT scan. It is difficult to discriminate from other multiple cystic lung diseases by imaging findings alone. However, almost all patients with BHD have characteristic skin and/or renal lesions and family history of pneumothorax, which can help differential diagnosis (8). LIP is most commonly associated with autoimmune disorders like Sjögren's syndrome or immunodeficiency. LIP is characterized by diffuse involvement of lung parenchyma by reactive pulmonary lymphoid tissue (6). Cysts in LIP may result from ischemia due to vascular obstruction, post-obstructive bronchiolar dilatation or bronchiolar compression by lymphoid tissues. Chest CT shows ground-glass opacities, centrilobular nodules, and cystic change (6). Cystic lung disease can be rarely associated with malignancy, typically metastasis from peripheral sarcomas and mesenchymal tumors (1, 7, 8). Cystic metastases due to sarcomas are often complicated by pneumothorax and portend a poor prognosis (9).

In our second case, multiple uniform round and thin-walled cysts were seen in both lungs with no lung nodules and involvement of bilateral costophrenic recesses, which prompted CT differential diagnosis of LAM even though a male gender of the patient. Unusual distribution of cystic lesions in both basal lungs and costophrenic recesses in PLCH was reported to be seen in pediatric population. However, it is very rare in adult population and only a few cases have been reported (10).

In conclusion, PLCH is a rare, multi-systemic disease with various and evolving radiological findings. Chest CT has proved to be of considerable value in the diagnosis and follow-up evaluation of PCLH with better prediction of disease activity. Radiologists can face various presentations of PLCH with atypical radiologic findings that correspond to the disease phase and temporal evolution. It forces radiologists to make differential diagnosis with other important lung diseases including malignancy and sometimes, it can be challenging to make correct diagnosis even for the experienced radiologists. With our case review, radiologists can be well aware of early and atypical CT presentations of PLCH. This will help to avoid unnecessary and invasive diagnostic procedures and improve prognosis of the patient with smoking cessation in a very early reversible stage.

Author Contributions

Conceptualization, R.K., H.J.H.; data curation, R.K., N.B.D., H.J.H.; formal analysis, R.K., N.B.D., H.J.H.; funding accquistion, K.D.W., P.Y.W., O.H.C., P.S.B.; investigation, all authors; methodology, R.K., N.B.D., H.J.H.; project administration, H.J.H.; resources, all authors; software, N.B.D.; supervision, H.J.H.; validation, K.D.W., P.S.B.; visualization, R.K., N.B.D., H.J.H.; writing—original draft, R.K., N.B.D., H.J.H.; and writing—review & editing, all authors.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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폐 랑게르한스 조직구 증식증의 비전형적 영상 소견: 2예에 대한 보고

유경화[1] · 남보다[1] · 황정화[1]* · 김동원[2] · 박영우[3] · 오홍철[3] · 박수빈[4]

폐의 랑게르한스 조직구 증식증은 드문 질환으로 주로 흡연력이 있는 젊은 성인 남성에서 발생한다. 이번 증례 보고는 폐 랑게르한스 조직구 증식증 2예에 대한 보고이며 이들은 모두 초기 검사에서 비전형적인 영상 소견을 보였다. 흉부 전산화단층촬영에서 폐 랑게르한스 조직구 증식증은 질환의 침범 정도와 시기에 따라 다양한 소견을 보일 수 있으며, 때로 악성 질환을 포함한 다른 중요 폐 질환들과 감별이 필요하고 영상 진단에 어려움을 줄 수 있다. 따라서, 이번 증례 보고를 통하여 폐 랑게르한스 조직구 증식증의 초기 및 비전형적인 영상 소견을 숙지함으로써 정확한 영상 진단에 도움을 주고 불필요하고 침습적인 검사를 줄일 수 있을 것으로 생각된다.

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