



Diffuse Large B-Cell Lymphoma Manifesting as Miliary Nodules in the Lung: A Case Report

폐의 좁쌀 결절로 발현된 림프종 사례: 증례 보고

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Malignant lymphoma has various pulmonary manifestations on chest CT, including nodules, masses, areas of consolidation, and ground-glass opacity. These presentations can pose a diagnostic challenge, as they mimic other disease patterns. Herein, we report a case of diffuse large B-cell lymphoma (DLBCL) manifesting as miliary nodules in a 67-year-old male initially presenting with dyspnea and fever. Radiologic findings included diffuse, bilateral, multiple tiny nodules consistent with metastasis, miliary tuberculosis, and fungal infection. However, further investigations, including laboratory tests, imaging, and biopsies, led to the diagnosis of DLBCL involving the lungs. Herein we reported a rare case of lymphoma involvement of the lung presenting as miliary nodules. Accurate diagnosis relies on a comprehensive evaluation of the clinical history, physical features, laboratory test results, and imaging findings.

Index terms Lymphoma; Miliary Tuberculosis; Miliary Nodule; Diffuse Large B-Cell Lymphoma

INTRODUCTION

Malignant lymphoma exhibits various pulmonary manifestations on chest CT, including nodules, masses, areas of consolidation, and ground-glass opacity. These lesions commonly show a peribronchovascular distribution with the perilymphatic interstitium (1, 2). These presentations can mimic various disease patterns. Lymphoma should be included in the differential diagnosis. This can pose a diagnostic challenge.

In the present case, radiologic findings included diffuse, bilateral, multiple tiny nodules

mimicking pulmonary metastasis, miliary tuberculosis (TB), and fungal infection. Similar reported cases (3, 4) have depicted such multiple nodular manifestations in patients with malignant lymphoma.

CASE REPORT

A 67-year-old male visited the emergency room because of dyspnea and fever. Laboratory tests revealed a reduced hemoglobin level of 8.7 g/dL (normal range: 13.5–17.5 g/dL) and an elevated C-reactive protein (CRP) level of 12.4 g/dL (normal range: 0–0.5 mg/dL). Chest and abdominopelvic CT (APCT) were performed because of fever. However, APCT revealed no abnormalities except mild hepatosplenomegaly.

The patient was admitted for anemia evaluation. He underwent a bone marrow biopsy and colonoscopy. The bone marrow biopsy revealed no abnormalities except a decreased cellularity of 10%–20%, which was categorized as hypocellularity considering the patient's age. No evidence of anemia, such as bleeding or a mass, was found on colonoscopy.

During hospitalization, the patient was treated with empirical antibiotics and symptomatic care for respiratory symptoms, which improved symptoms. His hemoglobin level had elevated. Subsequently, he was followed-up in the outpatient department. Two months after discharge, chest CT performed at an outpatient clinic because of recurrent fever revealed no abnormal findings. However, during the outpatient follow-up, the patient experienced recurrent dyspnea, chills, and fever for 4 months. Resultantly, he underwent repeated chest radiography and CT. At the time of the CT, his laboratory findings included a hemoglobin level 9.9 of g/dL (normal range: 13.5–17.5 g/dL), total leukocyte count of 4740/ μ L (normal range: 3800–10000/ μ L), and an elevated CRP level of 21.9 g/dL (normal range: 0–0.5 mg/dL). No definite evidence indicated decreased immunity.

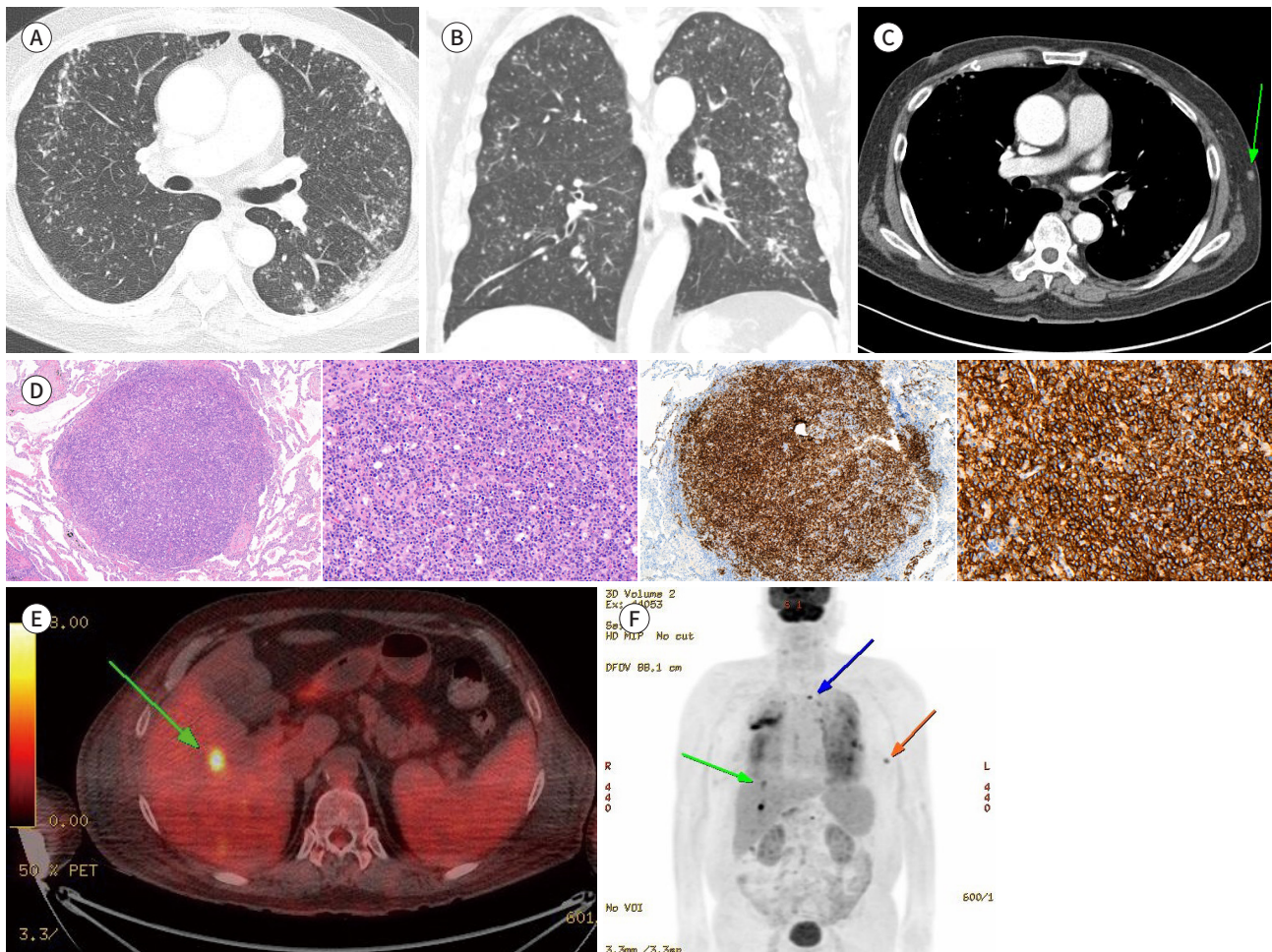
Four months after discharge (2 months after previous chest CT), miliary nodule deposits in both lung fields were found on chest radiography. Chest CT revealed innumerable, well-defined, miliary nodules varying in size, with a diameter of 1–7 mm, in a random distribution pattern and conglomeration. No tree-in-bud appearance or mediastinal lymphadenopathy was found (Fig. 1A, B).

Additionally, a small nodule was detected in the left lateral chest wall, which had increased in size since the last CT scan (Fig. 1C). This nodule was considered potentially indicative of soft tissue metastasis, soft tissue tumor, or breast tumor. Therefore, soft tissue or breast ultrasound was recommended.

As innumerable nodules of varying sizes were scattered in both lungs with random distribution, we considered hematogenous metastasis, military TB, and disseminated fungal infection in the differential diagnosis. Bronchoscopy was performed to obtain the definitive diagnosis. It revealed no invasive lesions in the bronchus. Acid-fast bacillus (AFB) culture and TB-polymerase chain reaction (PCR) for bronchial washing were also negative. As these lesions were new in onset compared to the CT scans acquired 2 months before, with no evidence of primary malignancy on previous APCT or chest CT, they were interpreted as infection, such as miliary TB or fungal infection, rather than hematogenous metastasis.

However, the following tests were negative: sputum smear for AFB and fungi, AFB culture

Fig. 1. A 67-year-old man with diffuse large B-cell lymphoma presents with miliary nodules in the lung.
A, B. Axial (A) and coronal (B) lung window chest CT images show tiny, small, well-defined, miliary nodules with a random distribution pattern, diameter of 1–7 mm, and conglomeration.
C. Axial mediastinal chest CT image shows no evidence of mediastinal lymphadenopathy but an enlarged nodule (arrow) in the left lateral chest wall.
D. Pathology of the right upper lobe shows diffuse infiltration by large atypical lymphoid cells with vesicular chromatin and prominent nucleoli (hematoxylin and eosin staining, × 100, × 400), and immunohistochemistry shows cells strongly positive for CD20 (immunohistochemistry staining, × 100, × 400).
E, F. Nodular lesion in liver segment 5 (E, arrow) and 7 (F, green arrow) show SUV max of 11.1 and 5.0 in each on ¹⁸F-FDG PET-CT. Other hypermetabolic lesions were also observed in the subcutaneous tissue areas of the upper back (SUVmax, 7.0) (blue arrow) and left lateral chest wall (SUVmax, 4.9; orange arrow).
 SUVmax = maximum standardized uptake value



of sputum, blood interferon- γ , and TB-PCR test of sputum. Bronchoalveolar lavage was also performed from the upper division of the left upper lobe and the lingular segment. Tests for the AFB strain, AFB culture, and TB-PCR using bronchioalveolar lavage were negative. Additionally, pneumonia PCR tests for *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Bordetella pertussis*, *Chlamydomphila pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae* also yielded negative results.

For the histological diagnosis, a video-assisted thoracic surgery biopsy was performed in the right upper lobe (RUL) to confirm the pathogen. The specimen was cultured for fungus

and TB. None of the cultures showed growth. The RUL specimen revealed infiltration of large atypical lymphoid cells with vesicular chromatin and prominent nucleoli. These atypical lymphoid cells were immunoreactive to CD20 and CD79a (Fig. 1D). DLBCL was definitively diagnosed.

Following the diagnosis, the patient underwent APCT and PET-CT for lymphoma staging. On APCT, newly developed ill-defined wedge-shaped or nodular lesions were seen in liver segments 5 and 7. These were absent in the initial CT scan acquired when he had visited the emergency room. These lesions showed hypermetabolic activity (maximum standardized uptake value; SUVmax, 11.1 and 5.0) on PET-CT (Fig. 1E). Hypermetabolic lesions were also observed in the subcutaneous tissue areas of the upper back (SUVmax, 7.0) and left lateral chest wall (SUVmax, 4.9), which were considered to be indications of lymphoma involvement (Fig. 1F). The patient was then started on R-CHOP chemotherapy. After the six cycles, the miliary nodules had completely disappeared on follow-up chest CT.

This study complies with the Declaration of Helsinki and written informed consent was obtained from the patient.

DISCUSSION

DLBCL is a group of aggressive B-cell lymphomas. It is the most common subtype of non-Hodgkin lymphoma (NHL). Extra-nodal disease occurs in 40% of cases, most commonly in the gastrointestinal tract (5). Secondary lung involvement by lymphoma is more common than primary lung involvement. Approximately 30%–40% of DLBCL cases secondarily involve the lung parenchyma, making it the most common subtype of NHL to do so (5, 6).

Lymphoma involving the lung typically manifests radiographically as a single or multiple nodules, masses, or areas of mass-like consolidation and ground-glass opacity (1, 2, 6). Even when lymphoma displays multiple nodular manifestations, the lesions are usually multiple small nodules rather than numerous subcentimeter tiny nodules. Lymphadenopathy is more frequently associated with Hodgkin lymphoma than with NHL (6). The present case showed no lymphadenopathy.

A random micronodular pattern is characterized by diffuse, centrally or peripherally located secondary pulmonary nodules. This pattern is considered indicative of hematogenous distribution of infectious or metastatic etiology, such as hematogenous metastases, or infections, such as miliary TB or disseminated fungal infections (7, 8).

The present and previous cases exhibited miliary nodules without a tree-in-bud appearance. These cases were considered miliary TB.

In a case described by Yagyu et al. (9), the patient presented with smaller pulmonary nodules that were more evenly sized compared to the present case. Moreover, nodules were found in the lungs and liver. Despite an initial consideration of liver nodules as a metastasis because of the patient's history of rectal cancer, further evaluation confirmed lymphoma (follicular lymphoma) involvement.

In another case described by Miyake et al. (10), centrilobular small nodules were presented with bilateral hilar and mediastinal lymphadenopathy. An open lung biopsy confirmed T-cell lymphoma.

Previous cases of lymphoma presenting with numerous nodules in both lungs include follicular and T-cell lymphomas (9, 10). This suggests that the presence of numerous tiny nodules is not associated with a specific subtype of lymphoma. Lymphoma cells can spread throughout the body via the peripheral blood and lymphatic system, reaching the lymph nodes, bone marrow, and gastrointestinal tract. This may facilitate hematogenous spread in the lungs, resulting in nodule formation.

When encountering a patient with numerous randomly distributed nodules on chest CT, a comprehensive evaluation of the patient's clinical history, laboratory findings, and other solid organ findings is essential. In cases without a definitive diagnosis or nodules not following a specific disease pattern, lymphoma involvement should be considered.

Author Contributions

Conceptualization, K.H.; supervision, K.H., K.S.S., P.H.K.; writing—original draft, N.H.J.; and writing—review & editing, K.H.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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REFERENCES

1. Angirish B, Sanghavi P, Jankharia B. Pulmonary manifestations of lymphoma: a pictorial essay. *Lung India* 2020;37:263-267
2. Sirajuddin A, Raparia K, Lewis VA, Franks TJ, Dhand S, Galvin JR, et al. Primary pulmonary lymphoid lesions: radiologic and pathologic findings. *Radiographics* 2016;36:53-70
3. Shinoda K, Taki H, Tsuda T, Hayashi R, Nomoto K, Tobe K. Primary pulmonary lymphoma presenting with multiple lung nodules. *Am J Respir Crit Care Med* 2014;190:e30-e31
4. Gao X, Yan P. Primary pulmonary lymphoma presenting as nodules and masses: a case report and literature review. *Monaldi Arch Chest Dis* 2021;91:1259
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019;69:7-34
6. Hare SS, Souza CA, Bain G, Seely JM, Frcpc, Gomes MM, et al. The radiological spectrum of pulmonary lymphoproliferative disease. *Br J Radiol* 2012;85:848-864
7. Andreu J, Mauleón S, Pallisa E, Majó J, Martínez-Rodríguez M, Cáceres J. Miliary lung disease revisited. *Curr Probl Diagn Radiol* 2002;31:189-197
8. Kim J, Dabiri B, Hammer MM. Micronodular lung disease on high-resolution CT: patterns and differential diagnosis. *Clin Radiol* 2021;76:399-406
9. Yagyu K, Kobayashi M, Ueda T, Uenishi R, Nakatsuji Y, Matsushita H. Malignant lymphoma mimics miliary tuberculosis by diffuse micronodular radiographic findings. *Respir Med Case Rep* 2020;31:101239
10. Miyake S, Yoshizawa Y, Ohkouchi Y, Kurashima A, Hebisawa A. Non-Hodgkin's lymphoma with pulmonary infiltrates mimicking miliary tuberculosis. *Intern Med* 1997;36:420-423

폐의 좁쌀 결절로 발현된 림프종 사례: 증례 보고

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악성 림프종은 흉부 CT에서 결절, 종양, 폐 경화, 간유리음영 등 다양한 폐질환으로 나타날 수 있으며 이러한 폐 병변은 다른 질환의 양상과 유사하여 진단에 어려움을 줄 수 있다. 본 증례는 호흡곤란과 발열을 주 증상으로 하는 67세 남성 환자로 해당 환자의 흉부 CT상 크기가 작은 다발성 결절이 양측에 미만성으로 나타나 혈행성 전이, 좁쌀 결핵 또는 진균 감염을 의심해 볼 수 있었다. 그러나 추가적으로 시행한 혈액 검사, 영상 검사 및 조직 생검 결과 폐를 침범한 미만성 큰 B세포 림프종이 진단되었다. 저자들은 폐의 좁쌀 결절로 발현한 매우 드문 림프종을 보고한다. 환자의 적절한 진단을 위해서는 환자의 병력, 신체 진찰, 혈액 검사 및 영상 소견의 포괄적인 평가가 필요하다.

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