SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2024; 41 (1): e2024008 DOI: 10.36141/svdld.v41i1.14700

Coexistent sarcoidosis mimics metastasis in a patient with early-stage non-small cell lung cancer: A case report

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Abstract. *Background and aim:* Sarcoidosis is a granulomatous disease. Malignant tumors are accompanied rarely by granuloma reactions that mimic metastasis. *Methods:* We present the case of a patient with possible advanced lung cancer with metastases to the mediastinal lymph nodes and bilateral ilia. *Results:* Ilium biopsy revealed the presence of sarcoid-like reaction. Bronchoscopy and endobronchial ultrasound revealed an adenocarcinoma in the right upper lung lobe, with a negative mediastinal lymph node. The correct staging of lung cancer was achieved through pathological examination of the surgically removed lung tissues. Two years later, the lung cancer metastasized, and the patient underwent systemic treatment. *Conclusions*: Coexistent sarcoid-like reaction may mimic metastatic lung cancer. A multidisciplinary approach and sequential diagnostic biopsies can prevent unnecessary surgery or inadequate treatment by distinguishing between coexistent sarcoidosis and metastatic lung cancer.

Key words: sarcoidosis, sarcoid-like reaction, non-small cell lung cancer, metastasis

Introduction

Sarcoidosis is a common systemic disease of unknown etiology that involves the formation of granulomas, and it is a multisystem inflammatory disease. The lungs are most frequently affected in sarcoidosis. Sarcoidosis, which mimics widespread metastatic cancer, has an exceptionally rare clinical manifestation involving the bone and has been documented in only a few instances (1). Here, we present a case of bone involvement with a sarcoid-like reaction in early-stage non-small cell lung cancer.

Received: 5 May 2023
Accepted: 31 October 2023
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Case presentation

In August 2018, a 57-year-old woman visited our clinic with a lingering cough that had persisted for 4 months. The patient was a nonsmoker. She had undergone surgery for thyroid cancer in 2010 and denied any history of pulmonary disease. Laboratory tests indicated no inflammation (C-reactive protein was 1.83 mg/L, erythrocyte sedimentation rate, 13 mm/h). Carcinoembryonic antigen (CEA) level was 1.5 ng/ml. Serum angiotensin-converting enzyme (ACE) levels were within the reference range (25 U/L); serum creatinine, alkaline phosphatase, and calcium levels were normal. A chest computed tomography (CT) scan performed immediately revealed a solitary cavitary lesion in the upper right lung, along with diffuse small perilymphatic nodules in both lungs and enlarged lymph nodes in the hilar and mediastinal regions. Pulmonary function test results were normal. In October 2018, fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT revealed slight uptake of 18F-FDG in the upper

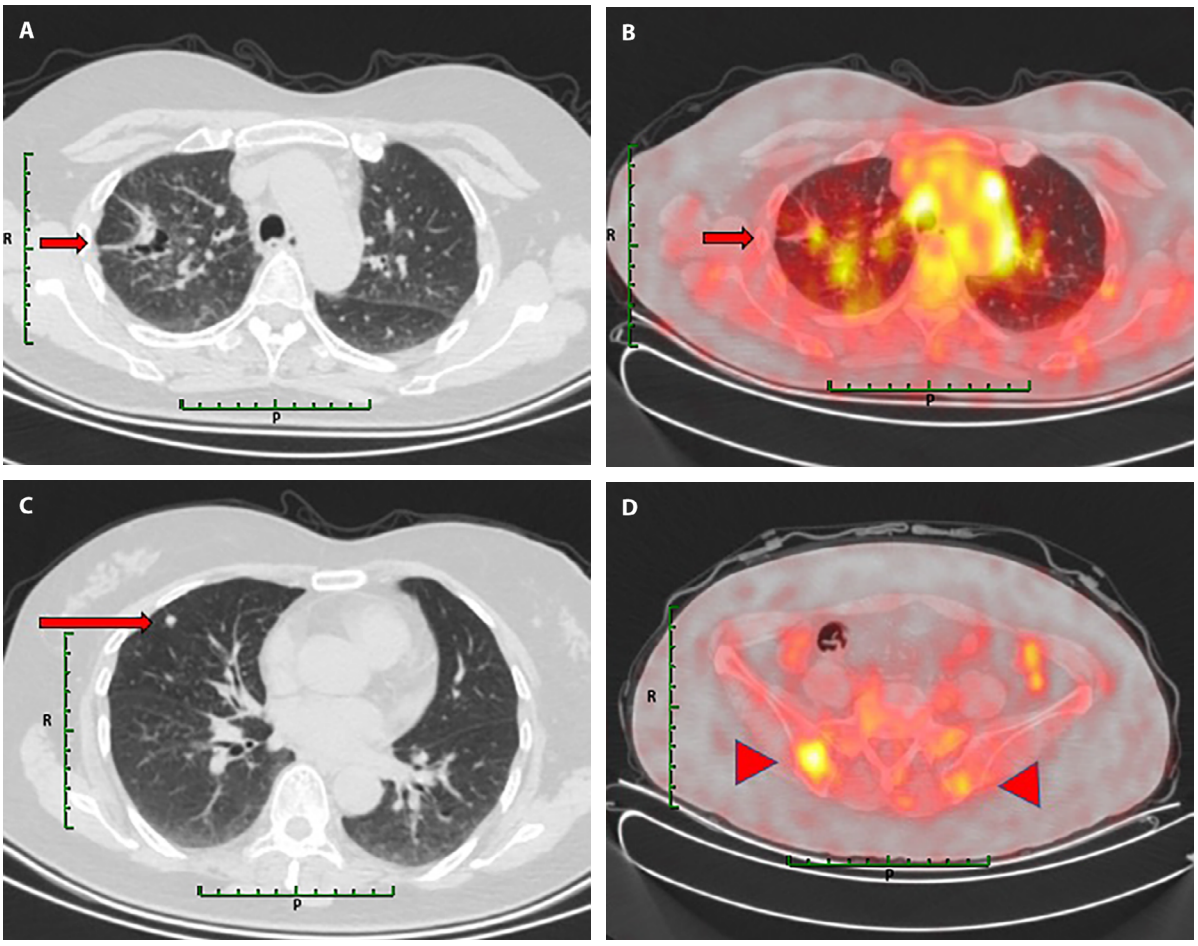

Figure 1. (A) and (B) A cavitary lesion in the right upper lung (maximum SUV, 2.6) (red short arrow), diffuse small perilymphatic nodules in both lungs, and enlarged hilar and mediastinal lymph nodes (maximum SUV, 8.5); (C) A small nodule measuring 5 mm in diameter in the right middle lobe (red short arrow); (D) Intense FDG uptake bilateral iliac (max SUV 4.6) (red triangle). Abbreviations: SUV: standardized uptake value; FDG: fluorodeoxyglucose.

right lesions and several lung nodules on both sides, with strong FDG uptake in the lymph nodes of the mediastinum and iliac regions (Figure 1). Magnetic resonance imaging revealed multiple bilateral osteolytic lesions that appeared to be bone metastases (Figure 2). Initially, the patient was diagnosed with advanced lung cancer and bone metastases (M1). However, biopsy of the ilium revealed epithelioid granulomas with small necrotic areas (Figure 3). Periodic acid–Schiff, acid-fast, and Grocott's methenamine silver staining yielded negative results. Therefore, the condition was diagnosed as possible sarcoidosis.

Bronchoscopy revealed multiple mucosal nodules in the right middle bronchus (Figure 4). The patient underwent radial endobronchial ultrasonography with a guide sheath and endobronchial ultrasound needle aspiration (EBUS). Pathological examination revealed adenocarcinoma in the upper right lung, non-necrotizing granulomas in the mucosa of the middle right bronchus, and no cancerous cells in the lymph nodes located at stations 4R and 7. No evidence of bacteria, fungi, or tuberculosis was found in the bronchoalveolar lavage fluid. Bronchoalveolar lavage showed cluster of differentiation (CD)4/CD8 ratio of 0.6 with 8% lymphocytes. Acid-fast bacillus staining and tuberculosis culture of the bronchoalveolar lavage fluid yielded negative results. The patient underwent resection of the right upper lobe of the lung and a part of the right middle lobe. Pathological analysis of the surgical specimen revealed adenocarcinoma with surrounding granulomas in the right upper lung lobe (Figure 5 A, B, and C), along with granulomatous nodules in the

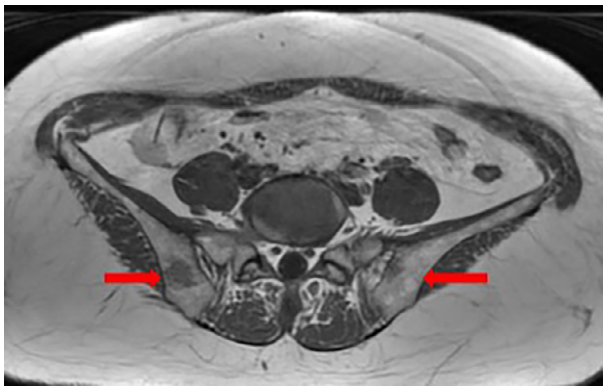

Figure 2. MRI of the ilium: MRI depicts bilateral multiple osteolytic bone lesions (red arrows). Abbreviations: MRI, magnetic resonance imaging.

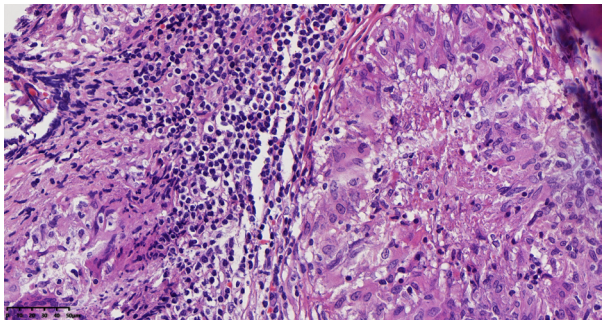

Figure 3. Histological microphotographs: ilium biopsy depicts epithelioid granulomas with small necrosis (HE, 40×HPF). Abbreviations: HPF, high-power field.

right middle lung lobe. The postoperative pathological stage was pT1N0M0, with an epidermal growth factor receptor (EGFR) mutation and a coexistent sarcoid-like reaction. Cardiac examination (electrocardiogram and cardiac ultrasound) revealed no involvement of the heart, whereas ophthalmological examination revealed no involvement of the eye.

In July 2020, chest CT displayed diffuse small perilymphatic nodules, and the hilar and mediastinal lymph nodes were larger than before (Figure S1). The ACE level was 46U/L, and the CEA level was 1.78 ng/ml. As an experimental treatment, methylprednisolone was administered initially at a dose of 40 mg/day, which was subsequently reduced to 5 mg/day for maintenance therapy over 6 months. In March 2021, chest CT revealed small diffuse perilymphatic nodules, hilar and mediastinal lymph nodes, and a solid nodule enlarging in the dorsal segment of the right lower lobe of the lungs (Figure S2). The CEA level increased to 19.34 ng/ml. The patient underwent icotinib therapy. After 3 weeks, she began experiencing fever with accompanying signs of respiratory distress. Bronchoscopy-obtained pathological tissue revealed a granuloma lesion, but no tumor. Numerous pleural, pericardial, and diaphragmatic metastases were identified during thoracoscopy. Pleural biopsy revealed adenocarcinoma with epithelial granulomas. She was administered osimertinib,

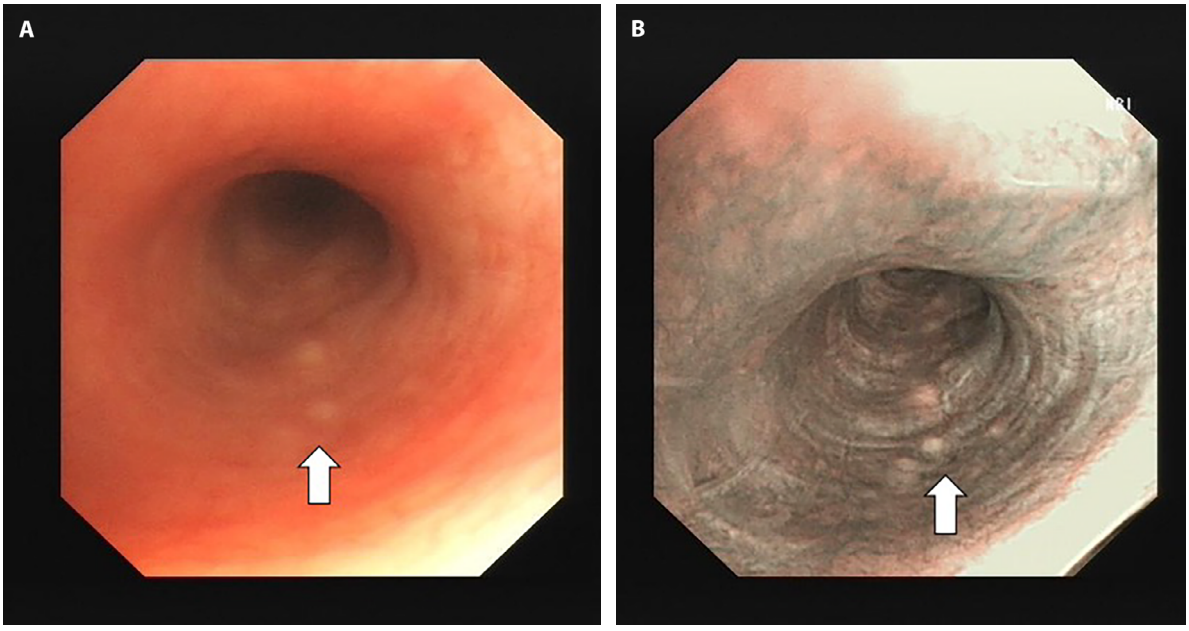

Figure 4. Bronchoscopy examination: bronchoscope depicts multiple mucosal nodules in the right middle bronchus (A. White light imaging, B. Narrow band imaging).

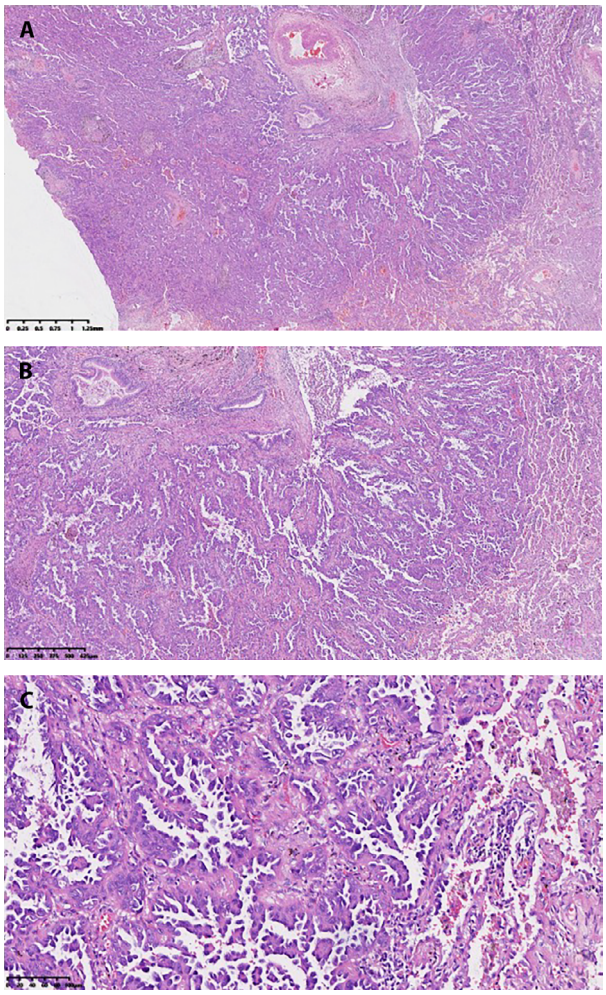

Figure 5. Histological microphotographs: surgical pathology shows adenocarcinoma with surrounding granulomas (A) (HE, 2×LPF). (B) (HE, 4×LPF). (C) (HE, 20×HPF). Abbreviations: HPF, high-power field.

and steroids were put on hold. A response evaluation conducted in August 2022 demonstrated that lung cancer and sarcoidosis remained stable (Figure S3). In January 2023, metastases were observed in the thoracic spine, lumbar spine, and ribs. The patient was diagnosed with metastatic lung cancer and received three cycles of carboplatin, pemetrexed, and bevacizumab. The latest evaluation was in May 2023 (Figure S4) with a partial response.

Discussion and conclusions

In this case, the patient was misdiagnosed with advanced lung cancer based on PET/CT findings. By contrast, the bone biopsy and EBUS results suggested an early stage malignancy, a sarcoid-like reaction involving the ilium, which was eventually confirmed by pathologic analysis of the surgically resected sample. Sarcoidosis is a multi-organ disease that manifests as non-caseating granulomas of an unknown etiology. Sarcoidosis can affect all organs to varying degrees. However, bone sarcoidosis is rare (3.4% of the studied population) (1), and such lesions are easily misdiagnosed as bone metastases. Bone biopsy is important for a precise diagnosis, considering the difficulty in distinguishing bone metastases from sarcoidosis using PET/CT and magnetic resonance imaging (2). During initial cancer diagnosis or suspected recurrence, histological evidence of non-caseous granuloma or sarcoidosis may be encouraging for patients. This leads to tumors being diagnosed at an early stage. The patient was diagnosed initially with adenocarcinoma involving sarcoidosis; however, we observed enlarged pulmonary and lymph nodes at the follow-up, which improved after experimental hormone therapy. Moreover, multiple metastases were observed. Researchers have reported on sarcoidosis or a sarcoidosis-like reaction to malignancy (3). This clinical case involved a systemic sarcoid-like reaction associated with cancer. The granulomatous reaction was initiated supposedly by cancer cells and perpetuated by persistent residual cancer cells, which led to metastatic disease. The increased granulomatous burden of previous tumors warrants considering the possibility of recurrence. Experimental corticosteroid treatment may temporarily improve the condition and mask tumor recurrence. Therefore, a differential diagnosis, especially of tumor or tumor recurrence, should be ruled out before diagnosing sarcoidosis.

It is unclear whether sarcoidosis predisposes the patients to malignancy or arises as an immune response to malignancy. Despite an unclear underlying mechanism, it may be related to long-term inflammatory reactions (4). Patients with sarcoidosis have a significantly increased risk of malignant tumors (5-7). Malignant tumors have been identified in patients previously diagnosed with sarcoidosis, either because the diagnosis was made based on the granulomatous response to malignant tumors, or because the treatment of sarcoidosis was associated with malignant tumors, or because sarcoidosis patients were essentially at risk for malignant tumors. Hence, individuals diagnosed with sarcoidosis must

undergo screening for cancerous tumors as a component of their initial assessment and subsequent medical monitoring (5-7).

However, there is no distinct association between lung cancer and sarcoidosis. Sarcoidosis can be detected in lung cancer lesions and in the hilar and mediastinal lymph nodes (8-10). Yamasawa et al. proposed that sarcoidosis and lung cancer coexist by chance. Lung cancer is associated with sarcoidosis-induced abnormal cell-mediated immunity. Sarcoidosis leads to fibrous tissue development, which is a source of lung cancer. Furthermore, its onset is caused by immunohistochemical reactions, which are responsive to malignant tumors (10). In this case, lung adenocarcinoma and sarcoidosis were observed simultaneously. Moreover, we observed granulomas in the pleural metastasis after tumor spread; hence, our patient could be cited as the fourth instance. She presented with bone sarcoidosis, in addition to lung cancer sarcoidosis reactions (8-10). Moreover, she harbored an EGFR mutation and responded to osimertinib treatment for 17 months. Kachalia et al. reported on a case of lung adenocarcinoma with an EGFR mutation and sarcoidosis. The patient was diagnosed initially with sarcoidosis and responded favorably to steroid therapy. Six months later, the lung adenocarcinoma had spread to the pleura, pericardium, and diaphragm, along with an EGFR mutation. After 6 months of erlotinib treatment, the disease progressed and palliative care was administered (11). Despite limited evidence for the association between sarcoidosis and lung cancer, clinicians should exclude metastatic malignant tumors from patients exhibiting clinical and imaging manifestations consistent with sarcoidosis.

$CD4^+$T cells are the predominant cell type in sarcoid granulomas and central to granuloma development, maintenance, and prognosis (12). Approximately two-third of patients with pulmonary sarcoidosis experience spontaneous remission. Patients in spontaneous clinical remission from sarcoidosis have fewer programmed cell death protein 1 (PD-1) + $CD4^+$T cells, with normal proliferative capacity of the T cells. Patients with clinical progress have five to six times higher PD-1+$CD4^+$T cells than do healthy controls, with reduced proliferative capacity (13,14). During PD-1 inhibition, the proliferative capacity of CD4+T cells returns to reference levels (13). PD-1 expression downregulation in CD4+T cells is associated with sarcoidosis regression, and PD-1 inhibitors are regarded as the therapeutic targets for sarcoidosis. However, PD-1 inhibitors can trigger sarcosis-like reactions (DISR). DISR is a systemic granuloma reaction that is difficult to distinguish from sarcoidosis (15). A delicate balance exists between immunosuppression and recovery of T cell function in sarcoidosis involving the PD-1 pathway, warranting further research.

This case emphasizes the need for a multidisciplinary team and sequential diagnostic biopsies to arrive at the correct diagnosis and avoid unnecessary surgery or insufficient treatment. Solid or hematologic malignancies are associated frequently with sarcoidosis, occurring prior to, during, or following disease onset. There are many circumstances in which diagnosis can be challenging and will require a careful diagnostic evaluation.

Conflict of Interest: The authors declare that they have no competing interests.

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Appendix

Supplementary file

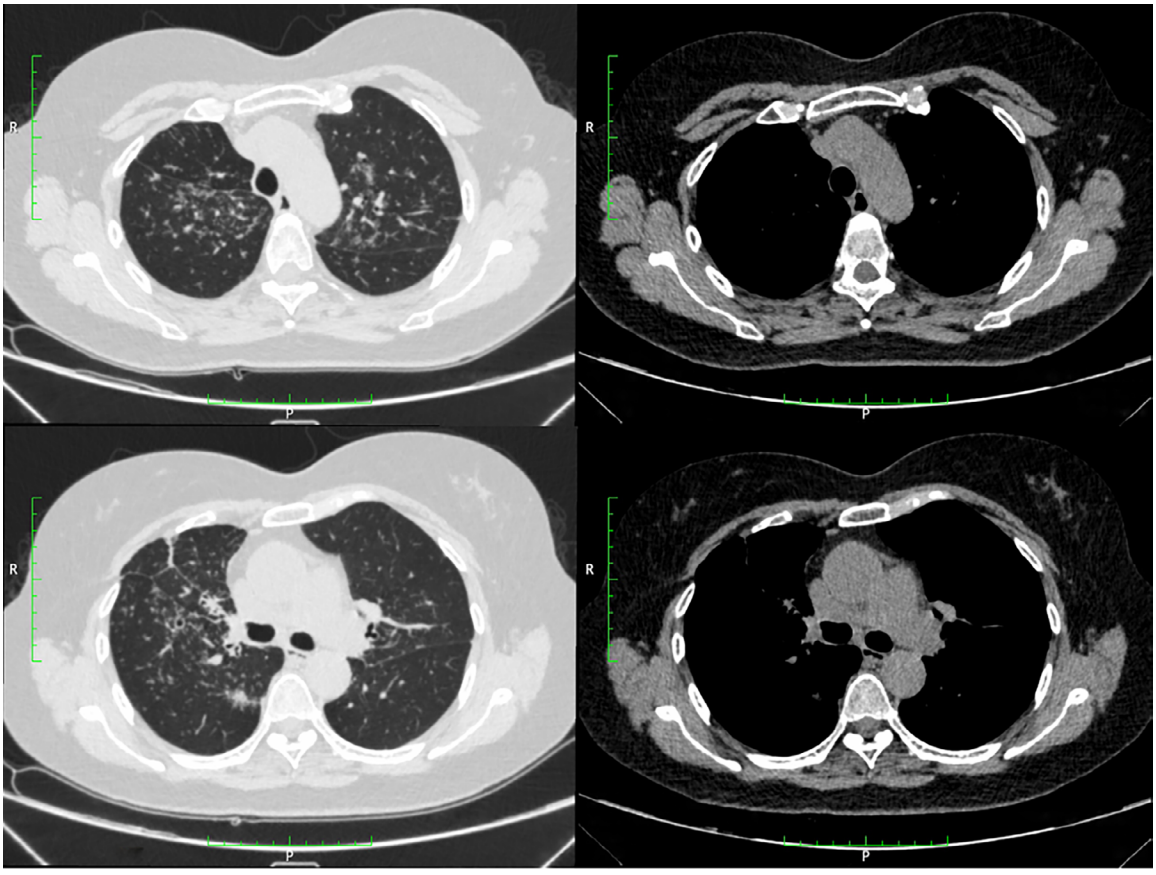

Figure S1. Chest computed tomography depicts that the diffuse small perilymphatic nodules, hilar and mediastinal lymph nodes are larger than before.

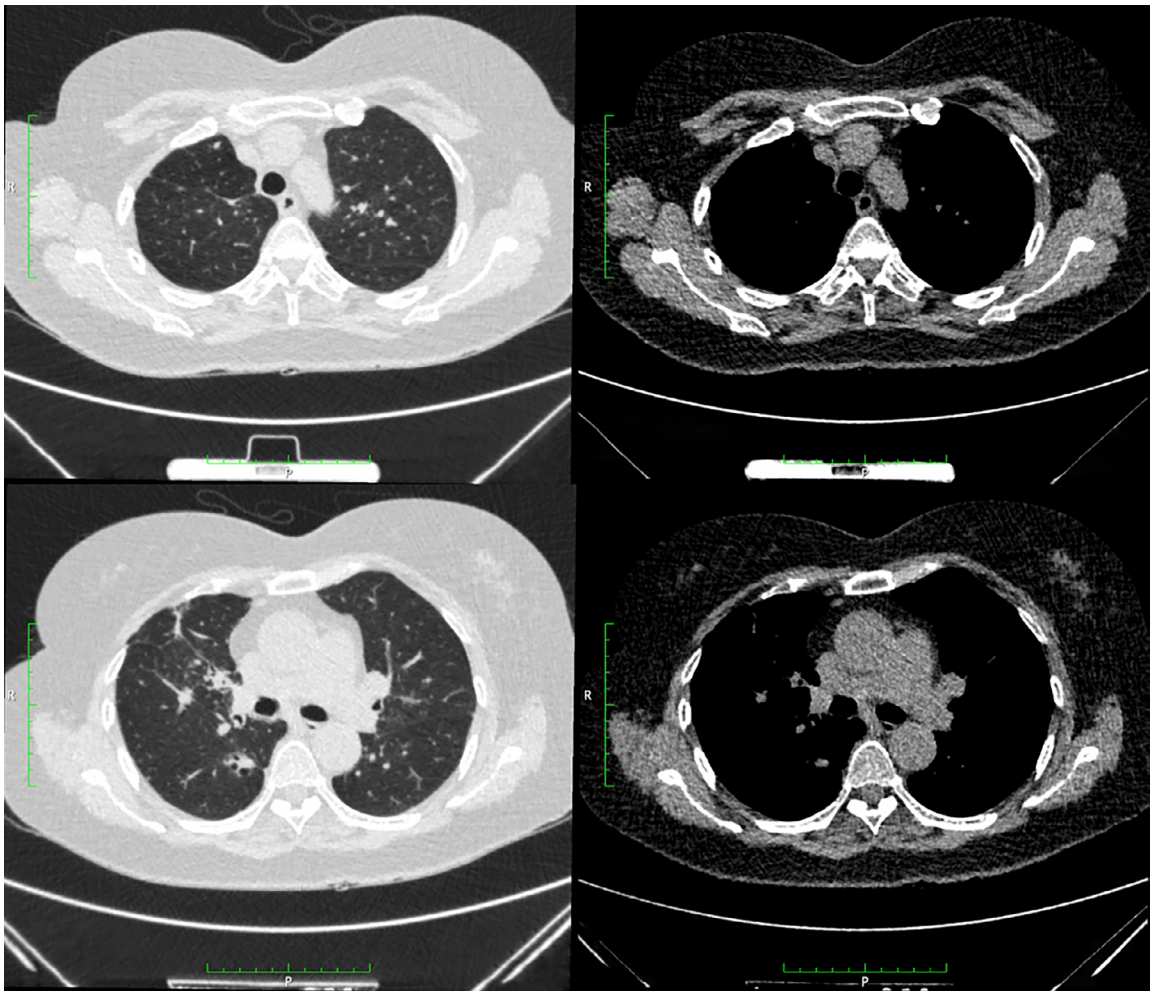

Figure S2. Chest computed tomography depicts shrinking diffuse small perilymphatic nodules shrinking, hilar, and mediastinal lymph nodes shrinking and an enlarging solid nodule in the dorsal segment of the right lower lobe of the lung.

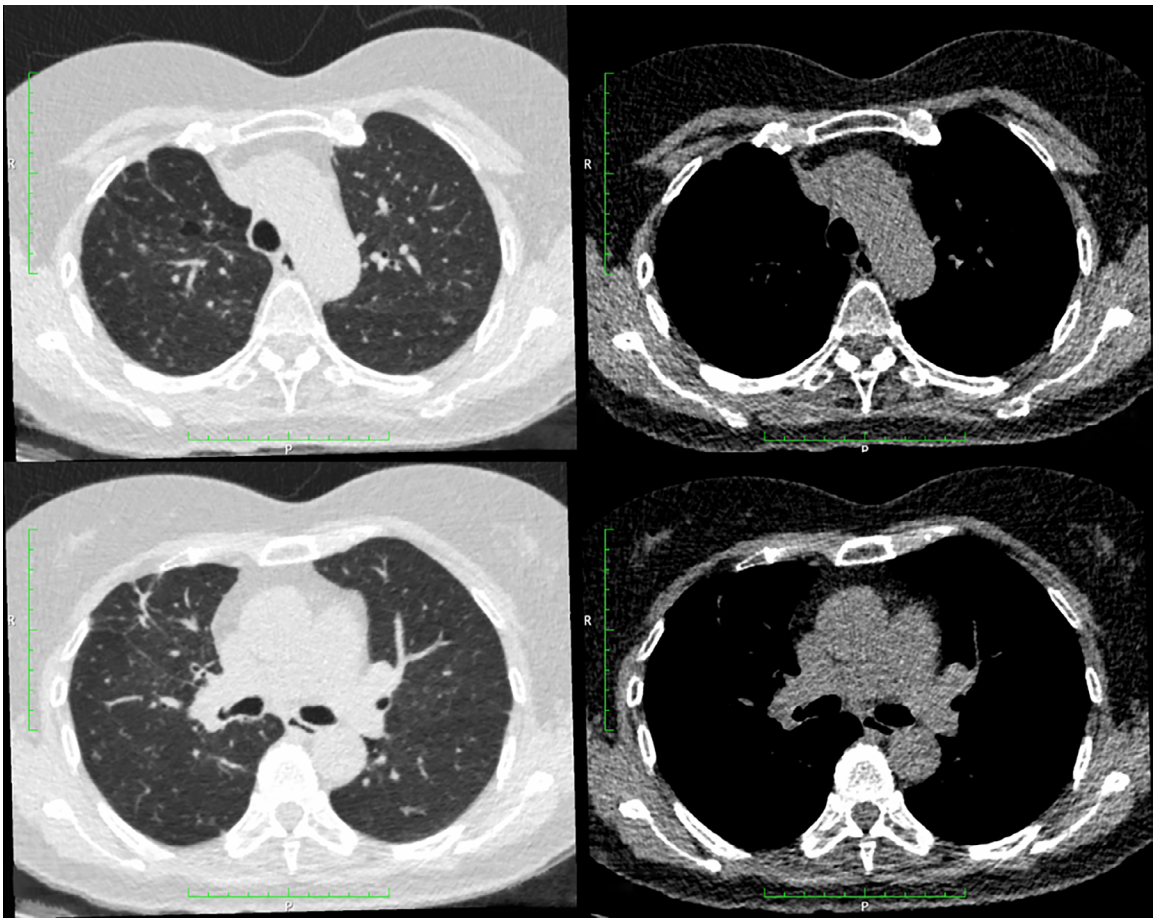

Figure S3. A response evaluation conducted in August 2022 shows stable lung cancer and sarcoidosis.

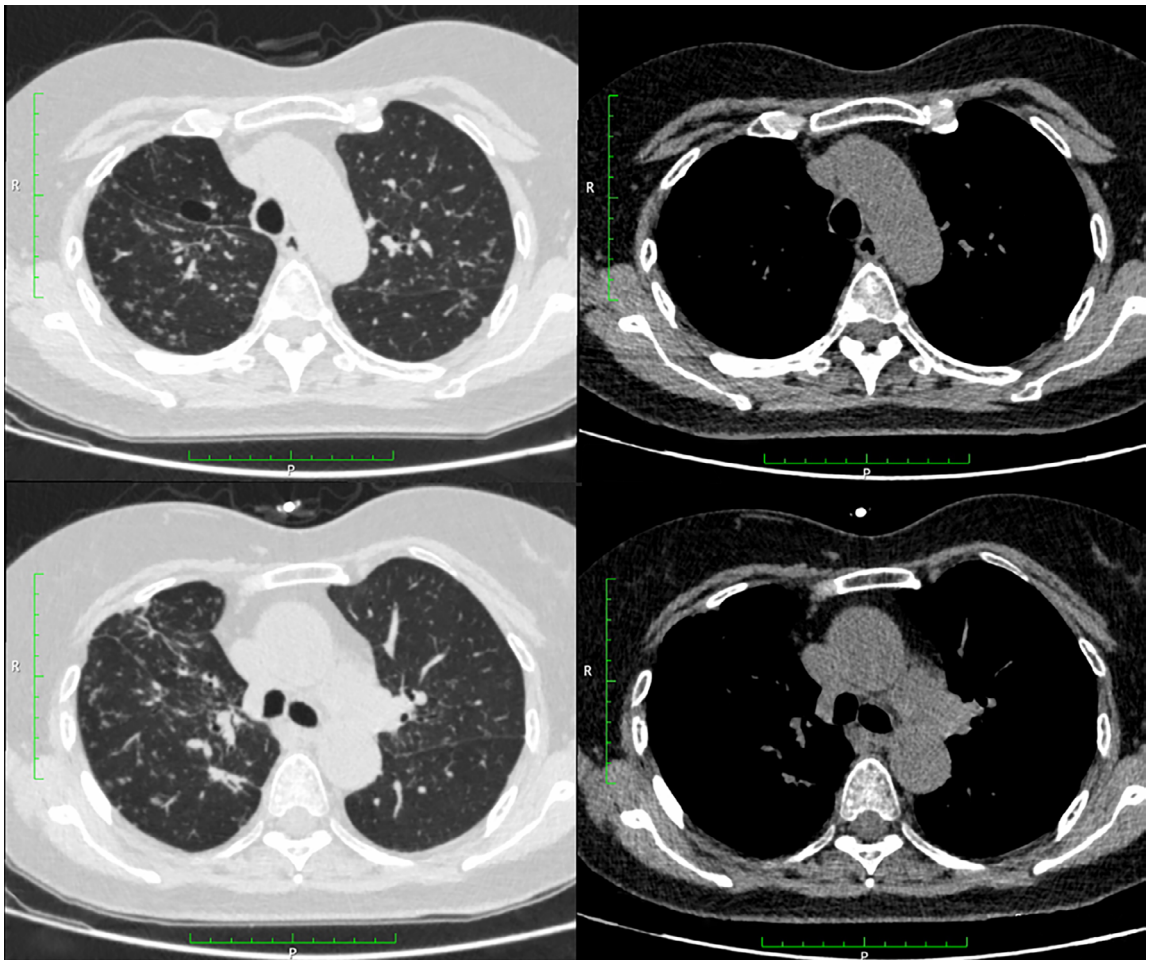

Figure S4. The most recent chest computed tomography in May 2023.