

## PULMONARY SARCOIDOSIS WITH LUNG INJURY INDUCED BY SHIN'ISEIHAITO

*Suzuki Kentaro<sup>1</sup>, Yoshiro Kai<sup>1</sup>, Masayuki Matsuda<sup>1</sup>, Kazuhide Horimoto<sup>2</sup>, Kazonori Iwai<sup>2</sup>, Eriko Hamada<sup>3</sup>, Yoshifumi Yamamoto<sup>3</sup>, Masato Takano<sup>4</sup> and Shigeo Muro<sup>3</sup>*

<sup>1</sup>Department of Respiratory Medicine, Minami-Nara General Medical Center, 8-1 Fukugami, Oyodo-cho, Yoshino-gun, Nara 638-8551, Japan; <sup>2</sup>Department of Internal Medicine, Yoshino Hospital, 130-1, Tanji, Yoshino-cho, Yoshino-gun, Nara 639-3114, Japan; <sup>3</sup>Department of Respiratory Medicine, Nara Medical University, 840 Shijo-cho, Kashihara City, Nara 634-8522, Japan; <sup>4</sup>Department of Diagnostic Pathology, Minami-Nara General Medical Center, 8-1 Fukugami, Oyodo-cho, Yoshino-gun, Nara 638-8551, Japan

To the Editor:

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. The th1-mediated immune reaction is essential for granuloma formation in sarcoidosis, which is more frequently localized in the lung, hilar/mediastinal lymph nodes, skin, liver, and eyes (1). Many patients with sarcoidosis remain asymptomatic and often experience spontaneous remission.

Lung involvement in sarcoidosis usually appears and slowly progresses, which leads to chronic interstitial lung disease with dyspnea. However, acute lung injury is uncommon (2).

Shin'iseihaito, which is a Japanese herbal medicine, has been widely used by Japanese general practitioners to treat patients with productive cough and acute and chronic bronchitis and is now available as an over-the-counter drug (3). Herein, we present a rare case of pulmonary sarcoidosis that mimics shin'iseihaito-induced acute lung injury in a patient whose symptoms and imaging findings rapidly improved after prednisolone (PSL) treatment. To the best of our knowledge, this is the first report of sar-

coidosis caused by the administration of a Japanese herbal medicine, such as shin'iseihaito.

A 72-year-old man with a history of cerebral infarction presented with dyspnea after 3 weeks of smoking cessation and shin'iseihaito treatment. He was referred and admitted to our hospital for further investigation and treatment.

Chest computed tomography (CT) revealed a lung infiltrative shadow primarily in the bilateral upper lobes and enlarged mediastinal and bilateral hilar lymph nodes (Figure 1A–E). A polymerase chain reaction test for coronavirus disease-2019 via nasopharyngeal swab was negative. He presented with a pulse rate of 133 bpm, temperature of 36.8°C, and blood pressure of 133/105 mmHg.

Arterial blood gas on room air analysis showed a PaO<sub>2</sub> of 72.1 Torr and PaCO<sub>2</sub> of 31.5 Torr. Laboratory data upon admission revealed high serum levels of Krebs von den Lungen-6 (991 U/mL) and surfactant protein D (560 ng/mL). His angiotensin-converting enzyme level was normal (15.3 IU/L) and his T-spot was negative.

Physical examination revealed bilateral fine end-inspiratory crackles at his lung bases. He was a current smoker (1.5 packs per day since 20 years old) with a history of asbestos exposure but without a history of bird rearing or familial interstitial lung diseases. Shin'iseihaito-induced lung injury was initially suspected after admission, and shin'iseihaito was discontinued. Empirically, he was treated with antibiotic

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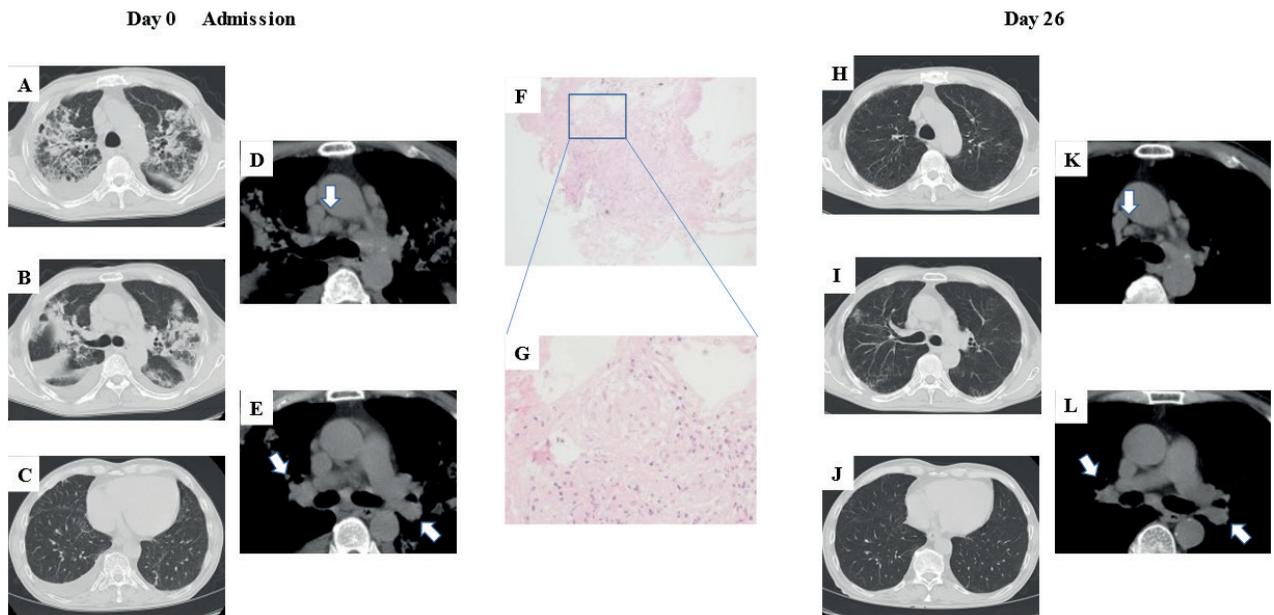
Correspondence: Yoshiro Kai

Department of Respiratory Medicine, Minami-Nara General Medical Center

8-1 Fukugami, Oyodo-cho, Yoshino-gun, Nara 638-8551, Japan.

E-mail: y-kai@eco.ocn.ne.jp

Tel: +81-747-54-5000, Fax: +81-747-54-5020



**FIGURE 1.** Chest computed tomography (CT) imaging on day 0 at admission (A–E). CT scan revealed bilateral lung infiltration and bilateral pleural effusion (A–C). Arrows indicate mediastinal and bilateral hilar lymph node enlargement (D and E). Histological examination of the TBLB specimen revealed noncaseating granulomas. (hematoxylin–eosin  $\times 40$  (F) and  $\times 200$  (G)). Chest CT after prednisolone administration on day 26 (H–L). Lung infiltrates disappeared (H–J), and the size of the mediastinal and bilateral lymph nodes was remarkably reduced (K and L).

therapy (ceftriaxone at 2 g/day) initially for 7 days. However, the inflammatory reaction and chest radiography findings did not improve. On day 7 after admission, he underwent bronchoscopy for bronchoalveolar lavage (BAL) fluid and transbronchial lung biopsy (TBLB) because the clinical course and imaging findings suggested the possibility of shin'iseihaito-induced pneumonitis. A drug lymphocyte stimulation test (DLST) for shin'iseihaito was negative. The BAL fluid (right B3) contained 90% of macrophages and 5% of lymphocytes, and an increased CD4/CD8 ratio (CD4/CD8 ratio = 2.76; reference range 1.2–1.8). TBLB of the right upper lobe showed inflammatory infiltrate and noncaseating granuloma (Figure 1F, G). Cultures from BAL fluid did not result in any bacterial, mycobacterial, or fungal growth and no cancer cells were detected. The ophthalmologist made a diagnosis of panuveitis although the patient did not complain of any ophthalmologic symptoms. Therefore, we diagnosed him with shin'iseihaito-induced sarcoidosis. He was treated with intravenous methylprednisolone (500 mg/day) for 3 days, followed by oral PSL at 40 mg/day for 7 days. Oral PSL intake was tapered to 30 mg/day for 7 days, and lung infiltrates were improved.

He was discharged on day 21. After discharge, PSL was tapered to 20 mg/day, the radiologic findings had disappeared, and enlarged mediastinal and bilateral hilar lymph nodes were remarkably reduced (Figure 1H–L). Follow-up chest X-ray after discharge confirmed the absence of recurrence.

DLST for shin'iseihaito was negative although the first clinical diagnosis due to bilateral lung infiltrates suggested drug-induced lung injury, and a lung biopsy was warranted to confirm the pulmonary sarcoidosis diagnosis. Bilateral panuveitis was also observed, and the presence of noncaseating granulomas demonstrated by pathological evaluation is typical in sarcoidosis (4).

Drug-induced lung injury due to herbal medicine was already reported in a study that included 73 Japanese patients (5). Bilateral ground-glass attenuations on chest CT and lymphocytosis with a low CD4/CD8 T-cell ratio in BAL fluid were common findings (5–7).

However, in this case, although increased lymphocytes were not detected, an elevated CD4/CD8 ratio in BAL fluid was observed. Moreover, other granulomatous disorders should be excluded (2).

Bacteria, fungi, and mycobacteria were not detected in BAL fluid or the TBLB specimen.

After administration of PSL, bilateral lung infiltrates were significantly improved and bilateral pleural effusion had largely resolved on chest CT. Pleural effusion may be associated with sarcoidosis (8). Sarcoidosis is characterized by a Th1-mediated inflammatory process for granuloma formation.

Shin'iseihaito inhibits the production of Th2 cytokines, such as interleukin-4, in an allergic murine model. Furthermore, shin'iseihaito increased the Th1 cytokine levels, such as interferon- (9).

Sarcoidosis does not generally cause a fulminant pulmonary syndrome. However, Gera et al. documented a case of sarcoidosis with acute respiratory distress syndrome (10).

Herein, we describe the first case of pulmonary sarcoidosis that presented as acute injury after shin'iseihaito administration. Acute lung injury is common after the use of herbal medicine, such as shin'iseihaito. However, these agents rarely cause conditions, such as sarcoidosis. Drug-induced lung injury was clinically suspected. Pulmonary sarcoidosis should be considered as a differential diagnosis in the case of bilateral lung infiltrates and enlarged mediastinal and bilateral hilar lymph nodes on chest CT.

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