

[ CASE REPORT ]

## Sarcoid-like Granulomatous Lung Disease with Subacute Progression in Silicosis

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### Abstract:

A 67-year-old man was admitted to our hospital with cough and fatigue. He had had long-term exposure to silica due to cement processing. Chest computed tomography showed bilateral centrilobular nodules, and hilar and mediastinal lymphadenopathy with calcification, suggesting chronic silicosis. Within a few months, these nodules enlarged, and bilateral patchy consolidations appeared. A lung biopsy revealed sarcoid-like granulomas with birefringent particles under polarized light without malignancy or infection. He was diagnosed with silicosis-associated sarcoid-like granulomatous lung disease, rather than sarcoidosis, according to the clinicopathological findings. His pulmonary manifestations improved after the discontinuation of silica exposure and combination therapy of corticosteroid and azathioprine.

**Key words:** sarcoid-like granulomatous lung disease, sarcoidosis, silicosis

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### Introduction

Silicosis is a fibrotic lung disease caused by the inhalation of free crystalline silicon dioxide or silica and is one of the most significant occupational diseases worldwide (1-3). There are three described forms of silicosis: chronic silicosis, accelerated silicosis, and acute silicosis (1-3). Chronic silicosis is the most common form, usually occurring with exposure to silica for  $\geq 10$  years, and the diagnosis is generally based on a history of substantial exposure to silica and compatible radiological features (1-3). There are also several other pulmonary conditions associated with silica exposure, including autoimmune diseases, malignant diseases, tuberculosis, chronic obstructive pulmonary disease, and sarcoidosis (1, 3).

Various environmental and occupational exposures have been related to sarcoidosis, and sarcoid-like granulomatous lung diseases that shows epithelioid granulomas pathologi-

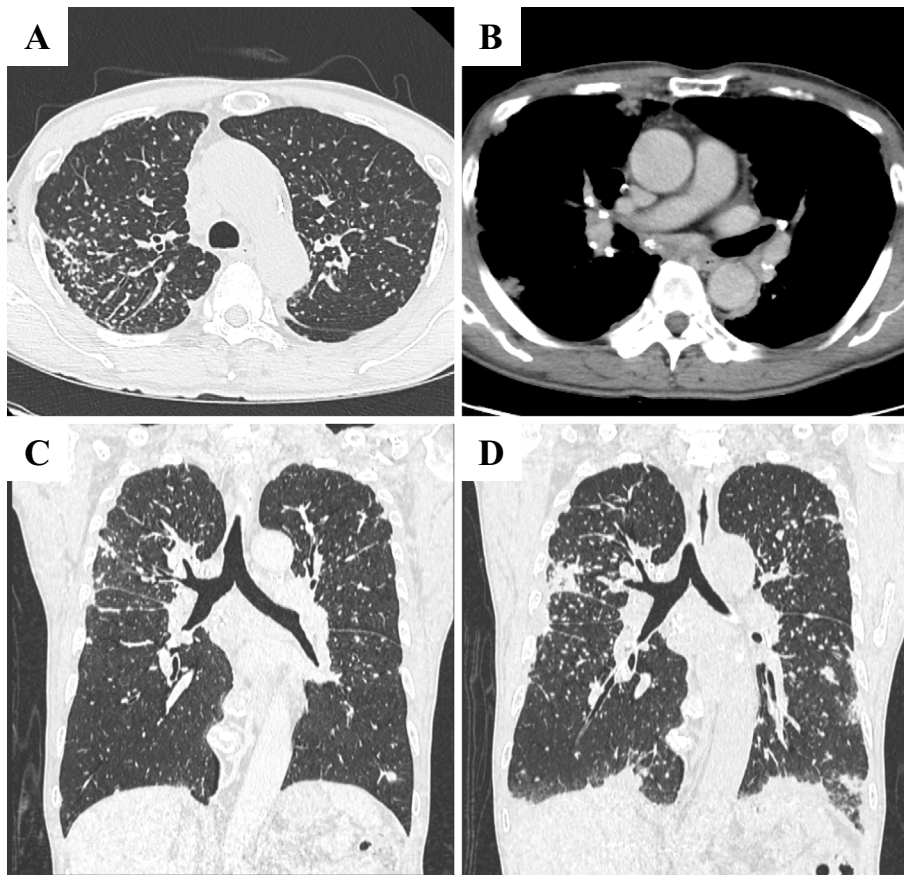
cally and clinically indistinguishable from pulmonary sarcoidosis (4-7). Inhalation of beryllium can cause granulomatous lung disease that mimics sarcoidosis (7), and other metals and inorganic dust have also been associated with a granulomatous response (4-6). Silica might be a trigger for sarcoid-like granulomatous lung disease, and several studies have reported the association between silica exposure and sarcoidosis or sarcoid-like granulomatous lung diseases (8-13).

We herein report a case of sarcoid-like granulomatous lung disease with subacute progression in silicosis. Although sarcoidosis was an important differential diagnosis, this case was diagnosed as chronic silicosis based on a history of long-term silica exposure and radiological findings, and it developed sarcoid-like granulomas containing birefringent particles under polarized light along these lesions, suggesting an association between silicosis and sarcoid-like granulomatous lung disease.

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**Figure 1.** Chest computed tomography shows multiple centrilobular nodules, predominantly in the bilateral upper lobes, and hilar and mediastinal lymphadenopathy with calcification, suggesting chronic silicosis (A-C). Within a few months, these lung nodules enlarged, and patchy consolidations appeared in the bilateral lung fields (D).

### Case Report

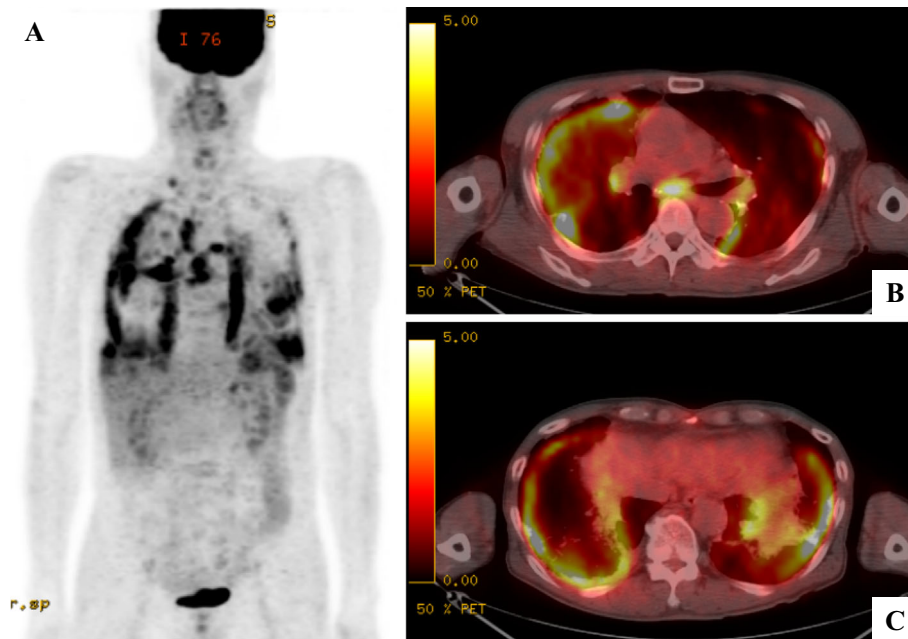
A 67-year-old Japanese man was admitted to our hospital with cough and fatigue. He was a current smoker (47 pack-years) until admission and had a medical history of hypertension. He had worked as a self-employed plasterer using cement compositions (mixing and applying cement for 8 h/day, no use of diatomaceous earth) without a dust mask for 49 years and had long-term exposure to silica due to cement processing. His work and smoking habits were unchanged before the onset of symptoms. There was no exposure to talc, mica, glass fibers, man-made mineral fibers (MMMF), or beryllium.

He was afebrile, and there was no evidence of skin rash, cervical or supraclavicular lymphadenopathies, arthralgia, or uveitis. Laboratory data showed an elevated white blood cell count (8,610/ $\mu$ L), C-reactive protein level (2.84 mg/dL), and soluble interleukin-2 receptor level (1,110 U/mL; normal range: 145-519). Serum findings of angiotensin-converting enzyme and tumor markers, including carcinoembryonic antigen, cytokeratin-19 fragments, and pro-gastrin-releasing peptide, were negative. An anti-glycopeptidolipid core IgA antibody assay kit for diagnosing *Mycobacterium avium*

complex and interferon-gamma release assays using ESAT-6 and CFP-10 antigens (T-SPOT<sup>®</sup>.TB) also showed negative findings.

Chest computed tomography (CT) showed bilateral centrilobular nodules, and hilar and mediastinal lymphadenopathy with calcification, suggesting chronic silicosis (Fig. 1A-C). Within a few months, these lung nodules enlarged, and patchy consolidations appeared in the bilateral lung fields (Fig. 1D). In addition, positron emission tomography/CT (PET/CT) demonstrated the uptake of <sup>18</sup>F-fluorodeoxyglucose (FDG) in the hilar and mediastinal lymph nodes, lung nodules, and bilateral subpleural consolidations with a maximum standardized uptake value (SUV<sub>max</sub>) of 7.3, 2.9, and 9.1, respectively (Fig. 2A-C). There was no significant FDG uptake in the extrathoracic lesions. Pulmonary function tests showed a preserved lung volumes and diffusion capacity: forced vital capacity (FVC), 3.58 L (99.7%) and diffusion capacity for carbon monoxide (DL<sub>co</sub>), 86.2%.

Bronchoalveolar lavage fluid revealed an increased lymphocyte percentage (66.0%) with a normal CD4/8 ratio of 1.16, and no growth was seen on culture. Histologically, endobronchial ultrasound-guided transbronchial needle aspiration from a mediastinal lymph node revealed dust-laden hyalinized collagen, consistent with silicosis (Fig. 3A), and a



**Figure 2.** FDG-PET maximum intensity projection (A) and FDG-PET/CT axial slices images (B, C) show a bilateral and symmetric abnormal uptake in hilar and mediastinal lymph nodes, lung nodules and bilateral subpleural consolidations with an SUV<sub>max</sub> of 7.3, 2.9, and 9.1, respectively. There was no significant FDG uptake in extrapulmonary lesions. FDG-PET/CT: <sup>18</sup>F-fluorodesoxyglucose positron-emission tomography/computed tomography, SUV<sub>max</sub>: maximum standardized uptake value

transbronchial lung cryobiopsy from the right upper lobe showed granulomatous inflammation with central partial necrosis (Fig. 3B). For the definitive diagnosis, a surgical lung biopsy from the right lower lobe was performed; it demonstrated multiple well-formed granulomatous lesions composed of clustered epithelioid cells and multinucleated giant cells, mainly around the bronchi, that were pathologically difficult to distinguish from pulmonary sarcoidosis, and lymphocytic inflammation was seen around the granulomas (Fig. 3C, D). Microorganism stains and cultures, such as acid-fast bacilli and fungi, were negative. An examination under a polarizing microscope showed birefringence particles in some sarcoid-like granulomatous lesions (Fig. 3E). Although an elemental analysis of biopsy samples was not performed, these findings suggested the association between silica exposure and sarcoid-like granulomas, since this case had no occupational exposure to metal dust, such as beryllium, except for silica exposure. Regarding the extrapulmonary lesions, there were no signs of cardiac, eye, skin, or neurological involvement. According to the clinicopathological findings, we diagnosed the patient with silicosis-associated sarcoid-like granulomatous lung disease, rather than sarcoidosis. None of the workers in the same workplace had symptoms or illnesses similar to this case.

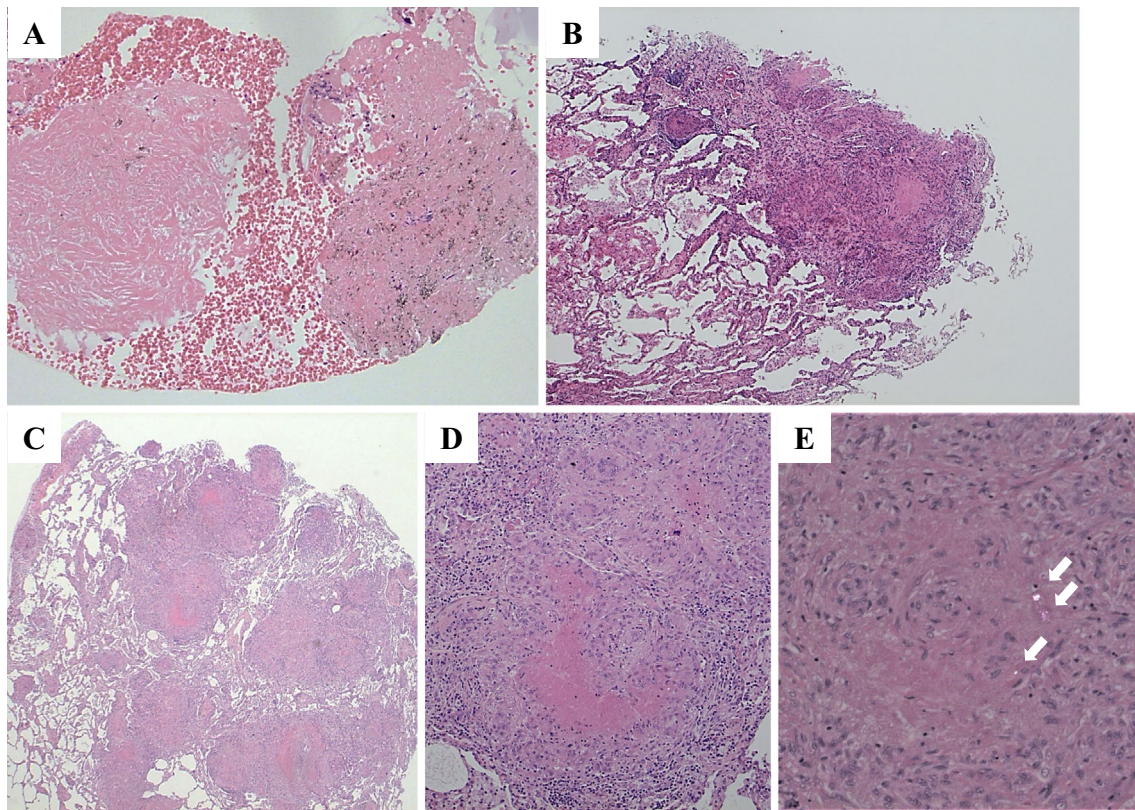
The clinical course after the surgical lung biopsy is shown in Fig. 4. After the diagnosis, we advised the patient to avoid further occupational exposure. The discontinuation of occupational exposure for approximately one month resulted a slight reduction of the multiple nodules in upper lung fields but no improvement of symptoms or lower lobe le-

sions. Therefore, we started corticosteroids (prednisolone 50 mg at 0.8 mg/kg/day) for subacute disease progression. The symptoms, lung shadows, and pulmonary function test findings gradually improved, but azathioprine was added during corticosteroid tapering because of the slightly worsening of radiological findings. Thereafter, the multiple nodules in both lungs shrank, and the consolidation on chest CT disappeared after nine months of treatment and cessation of occupational exposure.

## Discussion

In this report, we described a case of sarcoid-like granulomatous lung disease with subacute progression in silicosis. The patient had suffered significant silica exposure due to cement processing and showed chronic silicosis radiologically. Interestingly, the radiological findings considered to indicate silicosis worsened after a few months without any apparent incentive, and we confirmed sarcoid-like granulomas with small birefringent particles under polarized light after a biopsy. These pathologic findings were different from those of acute silicoproteinosis, accelerated silicosis, and rapidly progressive pneumoconiosis (1-3, 14, 15). Since the diagnosis of sarcoidosis is based on the exclusion other diseases, we diagnosed this case as silicosis-associated sarcoid-like granulomatous lung disease, rather than sarcoidosis, according to the clinicopathological findings. We believe that the present case may support an association between silicosis and sarcoid-like granulomatous lung disease.

Occupational and environmental factors have been impli-



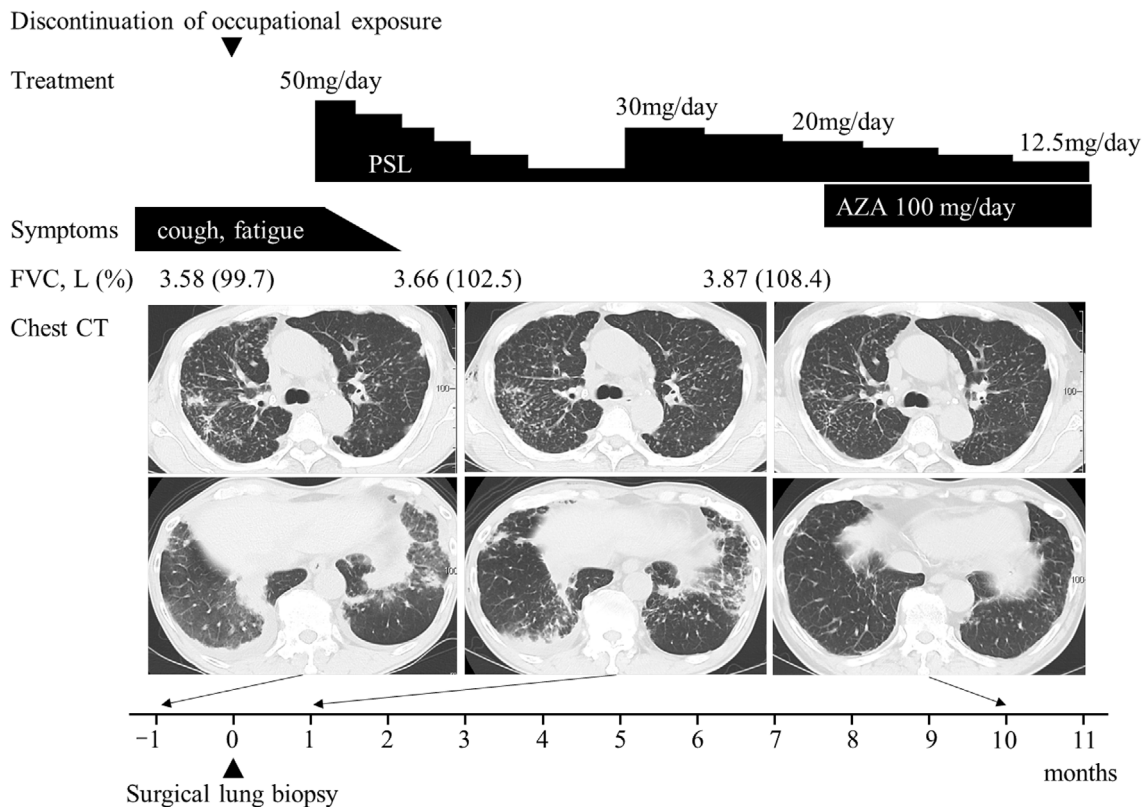
**Figure 3.** A histological examination of endobronchial ultrasound-guided transbronchial needle aspiration from mediastinal lymph node with Hematoxylin and Eosin staining shows dust-laden hyalinized collagen, consistent with silicosis (A:  $\times 75$ ). A transbronchial lung cryobiopsy from the right upper lobe shows granulomas consisting of epithelioid cells, lymphocytes, and central partial necrosis (B:  $\times 30$ ). A surgical lung biopsy from the right lower lobe demonstrates multiple sarcoid-like granulomatous lesions composed of clustered epithelioid cells and multinucleated giant cells, mainly around the bronchi, and lymphocytic inflammation was seen around the granulomas (C:  $\times 30$ , D:  $\times 150$ ), with several birefringent particles (arrows) noted in the granulomas under a polarizing microscope (E:  $\times 300$ ).

cated in sarcoidosis or sarcoid-like granulomatous lung disease (4-7). Inhalation of dust or fumes containing metals such as beryllium can cause granulomatous lung disease that mimics sarcoidosis (4-7). A previous report demonstrated that MMMF exposure was related to sarcoid-like granulomatous lung disease, and a quantitative analysis using electron microscopy of the granuloma from lung specimens showed the presence of silica, aluminum, and/or titanium, which are elements of MMMF (16). In addition, the incidence of sarcoid-like granulomatous lung diseases was reportedly increased among rescue workers with World Trade Center dust exposure, which was a heterogeneous exposure including dust, metal, and gas (17).

Silica exposure has been associated with sarcoidosis or sarcoid-like granulomatous lung disease (8-13). Epidemiological studies have noted a high incidence of sarcoidosis in patients with silica exposure (10, 11). Similar to the present case, several case reports have revealed that sarcoidosis or sarcoid-like granulomatous lung disease can occur in silicosis, and that it is difficult to distinguish between silicosis and sarcoidosis (12, 13). In the present case, a definitive di-

agnosis of chronic silicosis was made based on the history of long-term silica exposure and radiological findings, as well as the development of sarcoid-like granulomas containing birefringent particles under polarized light along these lesions considered to be silicosis. In addition, granulomatous infection was excluded because of the negative culture findings, including for acid-fast bacilli and fungi. These findings suggest that sarcoid-like granulomas are associated with silica exposure. Importantly, in cases with granulomatous lung disease and significant silica exposure, silicosis rather than sarcoidosis should be strongly suspected, and advice regarding cessation of further exposure should be provided (3).

The mechanism underlying sarcoid-like granulomatous lung disease in silicosis is unclear; however, silica or other inorganic dust may directly act as antigens (6). In an animal model, continuous low-dose silica exposure of rats caused granulomas with limited lung inflammation; however, acute exposure to high-dose silica caused granuloma-like lesions, severe alveolitis, and alveolar lipoproteinosis, suggesting a dose-dependent reaction (8, 18). In addition, immunoreactivity to silica and metals was found only in sarcoidosis pa-



**Figure 4.** The clinical course after the surgical lung biopsy. AZA: azathioprine, CT: computed tomography, FVC: forced vital capacity, PSL: prednisolone

tients using a lymphoid proliferation test, suggesting that in addition to beryllium, silica can also be considered a possible antigen (9). In contrast, silica exposure may act as an adjuvant signal triggering an immune response (6, 8). Silica dust may function as a “second hit” in addition to the “first hit” caused by exposure to microbial or other antigens (6, 8, 12). However, in the present case, no obvious cause of subacute progression was identified except for the likelihood of a transient increase in silica exposure.

At present, there is no effective treatment for silicosis (1-3). Following the diagnosis of silica-associated disease, the elimination of further exposure is generally recommended (1-3). In case reports of sarcoid-like granulomatous lung disease associated with silicosis, corticosteroid and/or azathioprine were effective in addition to elimination of silica exposure (12). Similar to these cases, in the present case, the discontinuation of silica exposure and combination therapy of corticosteroid and azathioprine resulted in improvement in the patient’s condition. In contrast, in another case report of sarcoidosis with silicosis, treatment with infliximab was effective, whereas a combination of corticosteroid and azathioprine was insufficient (13). Further evidence concerning the treatment of sarcoid-like granulomatous lung disease in silicosis should be collected. In the present case, it was suggested that subacute progression of sarcoid-like granulomas with inflammatory cell infiltration pathologically was associated with the need for immunosuppressive therapy in addition to avoiding silica exposure.

In conclusion, the findings of the present case support the association between silica exposure and sarcoid-like granulomatous lung disease, and the development of these diseases should be considered in the clinical course of chronic silicosis.

**The authors state that they have no Conflict of Interest (COI).**

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