

## Severe Pneumonitis with Alveolar Hemorrhage Associated with Herbal Medicines: A Case Report

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We report a case of pneumonitis with alveolar hemorrhage induced by herbal medicines in a 73-year-old woman who was admitted to our hospital because of dyspnea and an abnormal shadow on a chest radiograph. She had received treatment with numerous drugs, including the herbal medicines *Seisin-renshi-in*, *Chotosan*, *Rikkunshi-to*, and *Shakuyakukannzo-to*. Chest radiography revealed diffuse ground-glass shadows in both lungs, and bronchoalveolar lavage fluid was progressively hemorrhagic. A culture of the fluid showed no evidence of microorganisms. Moreover, there were no findings suggestive of rheumatic disease or vasculitides. On the basis of this evidence, we suspected drug-induced diffuse alveolar hemorrhage. She discontinued all medicines and started treatment with corticosteroids. Her respiratory condition and chest radiographic findings improved. The timing of administration and rechallenge with other drugs suggested that the herbal medicines were the causative drugs. The primary concern was *Seisin-renshi-in*, because it contains *Ougon* (skullcap; a known cause of pneumonitis) and because a drug lymphocyte stimulation test was positive for *Seisin-renshi-in*. This is the first report indicating that *Seisin-renshi-in* may cause diffuse alveolar hemorrhage. Diffuse alveolar hemorrhage due to herbal medicines is a rare but emergent disorder. Therefore, treating physicians should be aware that it may be caused by herbal medicines, including *Seisin-renshi-in*.

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**Key words:** drug-induced lung injury, alveolar hemorrhage, herbal medicine, *Seisin-renshi-in*

### Introduction

Numerous drugs, including herbal medicines, can induce pneumonitis. However, drug-induced pneumonitis is frequently overlooked, and it is often difficult to identify the causative agent. Approximately 150 types of herbal medicines for the treatment of various illnesses and symptoms are currently covered by Japan's health insurance system.

After a report of a death from interstitial pneumonia induced by *Sho-saiko-to*, physicians were warned of the risk of interstitial pneumonia induced by herbal medicines. Consequently, the package inserts of herbal medicines were revised, and the potential adverse effects associated with these agents were updated. Pneumonitis in-

duced by herbal medicines is characterized by various clinical features. Diffuse alveolar hemorrhage (DAH) is an emergent disorder; however, cases of DAH due to herbal medicines are rare. Nevertheless, cases of DAH caused by *Makyo-kanseki-to*<sup>1</sup> and *Sho-seiryu-to*<sup>2</sup> have been reported. In this report, we describe a case of severe pneumonitis suspected to be associated with DAH caused by herbal medicines.

### Case Report

A 73-year-old woman was admitted to Nippon Medical School Hospital, Tokyo, Japan, because of shortness of breath and cough. Before admission, a few days after onset of dyspnea, productive cough, and anorexia, she had

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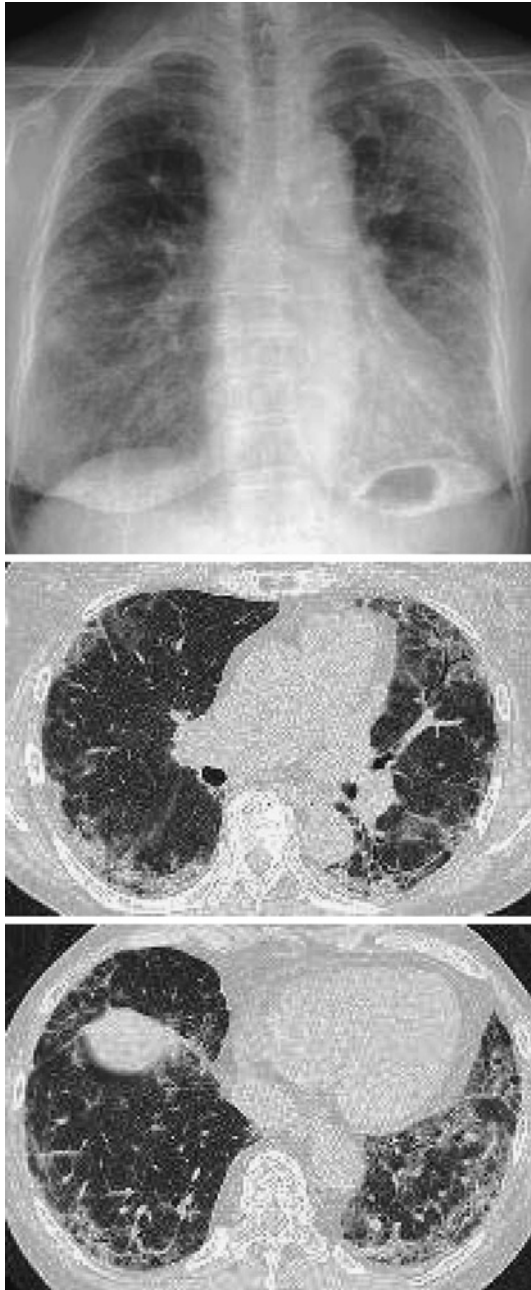


Fig. 1 Chest radiograph and computed tomography image at the time of admission show bilateral infiltrates and ground glass opacities.

a fever of 38°C. She was examined by a physician at another clinic 4 days later, and a chest radiograph showing a diffuse ground-glass shadow suggested a diagnosis of pneumonitis. She was referred to our hospital on the same day and immediately hospitalized.

The patient was taking multiple herbal medicines for management of dizziness and frequent urination, namely, Shakuyakukannzo-to (for 10 months), Rikkunshi-to (for 6 months), and Seisin-renshi-in and Chotosan (for 2 months). In addition, she had been receiving allopurinol, eicosapentaenoic acid, and alfalcidol for 10 months,



Fig. 2 Photograph of bronchoalveolar lavage shows progressive worsening of hemorrhage.

and nizatidine and zolpidem for 1 year, for treatment of hyperuricemia, dyslipidemia, and osteoporosis.

Physical examination showed a blood pressure of 135/71 mm Hg and a pulse rate of 82 beats/min. Auscultation revealed inspiratory fine crackles in the bilateral lower lung fields. Cardiac function was normal. Arterial blood gas levels were partial pressure of oxygen (PaO<sub>2</sub>) 66.9 Torr and partial pressure of carbon dioxide (PaCO<sub>2</sub>) 34.7 Torr, and pH 7.435. Laboratory testing of blood showed significantly elevated levels of white blood cells (WBC), C-reactive protein (CRP), lactate dehydrogenase (LDH), Krebs von den Lungen-6 (KL-6), and surfactant protein D (SP-D) (9,100 /μL, 10.21 mg/dL, 414 IU/L, 1,947.9 U/mL, and 106.7 ng/mL, respectively). The hemoglobin level decreased from 12.3 g/dL before disease onset to 10.7 g/dL after onset. Antinuclear antibody, rheumatoid factor, myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA), and proteinase 3 antineutrophil cytoplasmic antibody (PR3-ANCA) were negative. A radiograph and computed tomography (CT) image of the chest showed bilateral infiltrate and ground-glass opacities (Fig. 1). Bronchoalveolar lavage (BAL) was performed on the day of admission. Sequential BAL fluid of the left lower lobe was progressively hemorrhagic (Fig. 2). Moreover, differential cell analysis of the lavage revealed 19% alveolar macrophages, 18% eosinophils, 8% neutrophils, and 55% lymphocytes. The CD4/CD8 ratio of BAL fluid lymphocytes was 0.2. A culture of the fluid showed no microorganisms. Thus, pneumonitis associated with DAH was diagnosed. Of note, there were no findings suggestive of rheumatic diseases or vasculitides. An adverse drug reaction was suspected to be the

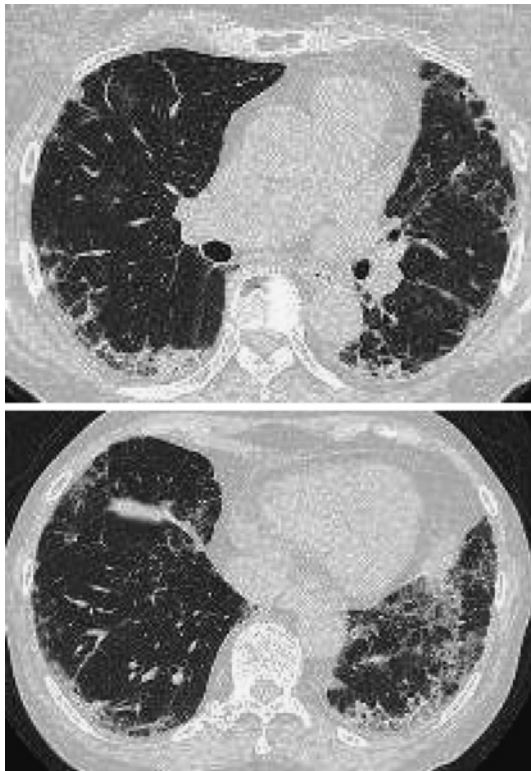


Fig. 3 Chest computed tomography image obtained on day 10 after hospitalization shows improvement in ground glass opacities and infiltrates.

cause of DAH.

After diagnosis, the patient discontinued all medicines, and intravenous methylprednisolone (1 g/day) was administered for 3 days. After treatment with methylprednisolone, peripheral oxygen saturation (SpO<sub>2</sub>) and chest radiographic images improved. On day 4 of hospitalization, the steroids were switched to oral prednisolone (1 mg/kg), and the dose was reduced by 10 mg per week. Chest CT on day 10 revealed improvement in ground-glass opacities and infiltrates (Fig. 3). Oxygen supplementation was discontinued on day 14 of hospitalization, and the patient was discharged on day 25. Treatment with zolpidem, eicosapentaenoic acid, and allopurinol was restarted after resolution of pneumonitis, but no symptoms developed. Drug lymphocyte stimulation tests (DLST) of Rikkunshi-to, Seisin-renshi-in, Chotosan, and Shakuyakukannzo-to yielded a positive reaction only to Seisin-renshi-in (Table 1).

### Discussion

Terada et al. reported that pneumonitis induced by herbal medicines generally developed within 2 months after the start of treatment<sup>3</sup>. Seisin-renshi-in and Chotosan were administered approximately 2 months before

Table 1 Results of drug lymphocyte stimulation testing (positive index is  $\geq 1.8$ )

Herbal medicine	Stimulation index
Chotosan	1.3 (-) negative
Rikkunshi-to	1.7 (-) negative
Shakuyakukannzo-to	0.98 (-) negative
Seisin-renshi-in	4.8 (+) positive

admission. In contrast, the other agents were administered more than 6 months before onset of symptoms. Moreover, Ougon (skullcap, an ingredient in herbal medicines) was reported to be an important cause of pneumonitis<sup>3</sup>. Among the herbal medicines used by this patient, Seisin-renshi-in was the only agent containing Ougon. In addition, a lymphocyte stimulation test was positive only for Seisin-renshi-in. Furthermore, pneumonitis did not develop after re-administration of any of the drugs that she had been using at the time of admission, other than the herbal medicines. Therefore, we believe that Seisin-renshi-in is the most likely cause of pneumonitis in our patient.

The clinical diagnosis of DAH was based on the presence of bilateral ground-glass opacities on chest CT and the fact that sequential BAL aliquots were progressively hemorrhagic. DAH has multiple causes, including connective tissue diseases, systemic vasculitides, glomerular diseases (i.e., Goodpasture's syndrome), coagulation disorders, and drug toxicity<sup>4,5</sup>. Physical and laboratory examinations of our patient did not yield positive findings for collagen vascular diseases or glomerular diseases, and blood coagulation tests were unremarkable. Therefore, DAH in our patient was likely attributable to another cause (i.e., drug-induced DAH).

DAH is a clinicopathological syndrome associated with accumulation of intra-alveolar erythrocytes originating from alveolar capillaries<sup>6</sup>. Because DAH can be life-threatening, early diagnosis and identification of its cause are essential. Although hemoptysis is one of the main symptoms of DAH, it is initially absent in up to 33% of cases, as in the present patient<sup>6</sup>. Other symptoms are nonspecific and include fever, chest pain, cough, and dyspnea. Chest radiographic findings are also nonspecific and consist of a patchy, focal, or diffuse alveolar filling process<sup>6</sup>. A clinical diagnosis of DAH is confirmed when sequential BAL aliquots from the same location are progressively hemorrhagic and the presence of infection can be excluded<sup>4</sup>. Numerous drugs and toxins have been linked to DAH development, including crack cocaine,

Table 2 Clinical characteristics of interstitial lung disease induced by Seisin-renshi-in

Case	Age Gender	Duration of administration	WBC /uL	CRP mg/dL	LDH IU/L	KL-6 U/mL	DLST	Treatment	Outcome
Tagawa [11]	68 M	2 weeks	11,600	12.6	ND	ND	Positive	Drug cessation	Improved
Nagato [12]	83 M	10 days	7,250	16.88	603	1,130	Positive	Drug cessation Corticosteroid	Expired
Nogami [13]	79 M	2 months	4,300	0.2	289	1,744	ND	Drug cessation	Improved
Tsukakoshi [14]	82 F	3 months	8,600	4.16	287	404	Negative	Drug cessation	Improved
Yokomura [15]	54 F	11 days	4,620	28.8	250	324	Negative	Drug cessation	Improved
Yokomura [15]	80 M	6 months	6,340	1.2	281	8,660	ND	Drug cessation	Improved
Toyoshima [16]	62 M	45 days	12,100	10.2	470	1,580	Positive	Drug cessation Corticosteroid	Improved
Haga [17]	74 M	2 weeks	10,100	12.77	296	202	Positive	Drug cessation Corticosteroid	Improved
Ishimoto [18]	72 F	2 months	6,500	0.16	290	3,280	Positive	Drug cessation	Improved
Ogata [19]	70 F	20 days	9,100	11.61	339	612	Positive	Drug cessation	Improved
Present case	73 F	2 months	9,100	10.21	414	1,947.9	Positive	Drug cessation Corticosteroid	Improved

Abbreviations: WBC: white blood cells, CRP: C-reactive protein, LDH: lactate dehydrogenase, KL-6: Krebs von den Lungen-6, DLST: drug lymphocyte stimulation test, ND: no data.

trimellitic anhydride, isocyanates, D-penicillamine, warfarin, nitrofurantoin, propylthiouracil, clopidogrel, fibrinolytics, aspirin, amiodarone, phenytoin, carbamazepine, methotrexate, mitomycin C, radiographic contrast media, and cytotoxic drugs<sup>4</sup>. However, DAH rarely develops after administration of herbal medicines.

General herbal medicines, which are widely prescribed in Japan, consist of multiple herbal ingredients. Currently, the pharmacological mechanisms of herbal medicines are not well understood, and hepatic dysfunction and lung injury are established adverse events caused by herbal medicines<sup>3</sup>. Although the exact mechanisms of these adverse events are unclear, hypersensitivity is considered a primary cause<sup>3</sup>. In 1989, Tsukiyama et al. reported the first case of pneumonitis induced by Sho-saiko-to<sup>7</sup>, which was followed by reports of lung injury (including deaths) induced by Sho-saiko-to<sup>8</sup>. This has become a serious social concern in Japan<sup>9</sup> and has led to the introduction of guidelines for the safe use of Sho-saiko-to<sup>10</sup>.

Several cases of pneumonitis induced by herbal medicines were later reported, notably, 10 cases of interstitial lung disease induced by Seisin-renshi-in<sup>11-19</sup> (Table 2). The interval to disease onset in these reports varied from 10 days to 6 months. Moreover, elevations in white blood cell count (five cases), eosinophil count (four cases), KL-6 (six cases), CRP (eight cases), LDH (five cases), and hepatic dysfunction (five cases) were observed. Eight patients underwent DLST. Positive reactions to Seisin-renshi-in were observed in five cases, and a suspected

positive reaction was observed in one patient<sup>12</sup>. Among the five positive cases, the test result was negative during corticosteroid therapy but became positive after the start of corticosteroid therapy in a case reported by Haga et al.<sup>14</sup>. Nine cases progressed mildly and improved after cessation of drugs and/or after corticosteroid therapy. In 2013, Nagato et al.<sup>12</sup> reported diffuse alveolar damage induced by treatment with Seisin-renshi-in. In addition, Toyoshima et al. reported lymphocytic infiltration of alveolar septa, desquamative alveolar lining cells, and fibrinous exudate in alveolar spaces<sup>16</sup>. Tagawa et al.<sup>11</sup> reported hypertrophy of alveolar epithelium and interstitial fibrosis.

This is the first reported case of alveolar hemorrhage induced by treatment with Seisin-renshi-in.

Kondo reported that, in Japan, the DLST positive rate was 66.9% and 67.6% for drug-induced lung disease (DILD) caused by medicines and herbal medicines, respectively<sup>20</sup>. Furthermore, Enomoto et al. reported that the DLST positive rate for cases of DILD caused by Japanese herbal medicines was 56%<sup>21</sup>. DLST is a noninvasive examination tool for auxiliary diagnosis of DILD. However, it is limited by the high risk of false-positive results and the weak correlation between positive DLST results and drugs suspected to induce pneumonitis<sup>3,22,23</sup>. A previously reported problem is that, although lymphocyte reactions differ, the same reference value is used for all drugs<sup>18</sup>. In addition, treating physicians should take into account that corticosteroid therapy may induce false-negative results in DLST<sup>17</sup>. Therefore, future studies

should attempt to determine the usefulness of DLST in DILD diagnosis.

Herbal medicines can cause adverse effects, and deaths from pneumonitis caused by herbal medicines have been reported. The risks of adverse drug reactions (including DILD) should be explained to patients, and they should be advised to consult their physicians if symptoms (e.g., cough, fever, and dyspnea) develop after starting treatment with herbal medicines. The clinical history and medication records of patients presenting with pneumonitis should be evaluated, especially if they are treated with multiple agents. Reaching a definitive diagnosis of DILD is often difficult. However, prompt action, including discontinuation of treatment, is necessary in patients at high risk of developing DILD.

### Conclusion

We reported a case of severe pneumonitis with DAH in a patient receiving treatment with four herbal medicines. Seisin-renshi-in was the most likely cause of pneumonitis. Given the wide use of herbal medicines, treating physicians should recognize these agents as a potential cause of pneumonitis with DAH.

**Conflict of Interest:** The authors have declared no conflict of interest.

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