□ CASE REPORT □

# Pneumonitis Caused by Saikokeisikankyou-tou, an Herbal Drug

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**A 57-year-old man was admitted to our hospital because of dyspnea and abnormal shadow on chest roentgenogram. He had received two herbal drugs: Saikokeisikankyou-tou (SKT) for one month and Licium Halimifolium Mil (LHM) for two weeks. After admission, all medication was stopped and his symptoms were gradually diminished. Transbronchial lung biopsy specimens showed interstitial pneumonia. Lymphocyte stimulation test, skin test and challenge test were positive to these herbal drugs. We diagnosed him as drug-induced pneumonitis. This is the first report on pneumonitis caused by Saikokeisikankyou-tou diagnosed by lymphocyte stimulation test, skin test and challenge test.**
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***Key words:*** drug induced pneumonitis, herbal drug, lymphocyte stimulation test

## Introduction

Many types of drugs are known to cause pneumonitis. Herbal drugs sometimes cause pneumonitis and most of the reported cases are caused by Shousaiko-tou. Saikokeisikankyou-tou is a complex of several substances including Saiko, Ougon, and Keisi. We describe a patient with pneumonitis caused by Licium halimifolium Mil and Saikokeisikankyou-tou diagnosed by positive lymphocyte stimulation test, skin test and challenge test.

## Case Report

A 57-year-old man was admitted to Toyama Red Cross Hospital on Nov. 29, 1994 for shortness of breath, cough and fever. Because he had caught a recent cold, he visited an oriental medicine practitioner and was prescribed Saikokeisikankyou-tou on Oct. 28, 1994 and then Licium halimifolium Mil was dispensed to the patient 18 days later. He had taken these drugs in a low dose. These drugs were increased to their standard doses 13 days later. On that day he developed dyspnea, cough, and fever, and was admitted to our hospital.

On physical examination, his blood pressure was 146/96 mmHg, pulse rate was 82 beats/min, and respiratory rate was 24/min. On uscultation he had late inspiratory fine crackles over the bilateral lower lung fields. Cardiac examination was normal.

On admission, the arterial blood gas levels revealed the following: $PaO_2$, 67.5 mmHg; $PaCO_2$ 39.3 mmHg; pH 7.41. The differentiation of white blood cell count was 66.6% neutrophils, 5.4% monocytes, 18.2% lymphocytes, and 9.5% eosinophils. The C-reactive protein (CRP) was 4.9 mg/dl and total protein was 5.7 g/dl. A chest roentgenogram (Fig. 1a) and a chest computed tomography (CT) (Fig. 1c) revealed bilateral infiltrates in the lower lung fields.

After admission, both drugs were stopped and piperacilline sodium (4 g/day) was given intravenously. The day after admission, his symptoms diminished and chest roentgenogram showed an improvement (Fig. 1b).

Pulmonary function test performed on Dec. 3 showed normal values with a vital capacity of 3.3 *l* (93.5% of predicted), a forced expiratory volume in one second of 2.3 *l* (76.3% of predicted), a single breath carbon monoxide diffusion capacity of 3.92 ml/min/*l* (83.3% of predicted). $^{67}Ga$ scintigraphy on Dec. 5 revealed no abnormal accumulation in the lungs. On Dec. 6, bronchoalveolar lavage (BAL) was performed using a total volume of 100 ml of sterile saline solution (35% recovery). Differential cell analysis revealed 66.4% alveolar macrophages,

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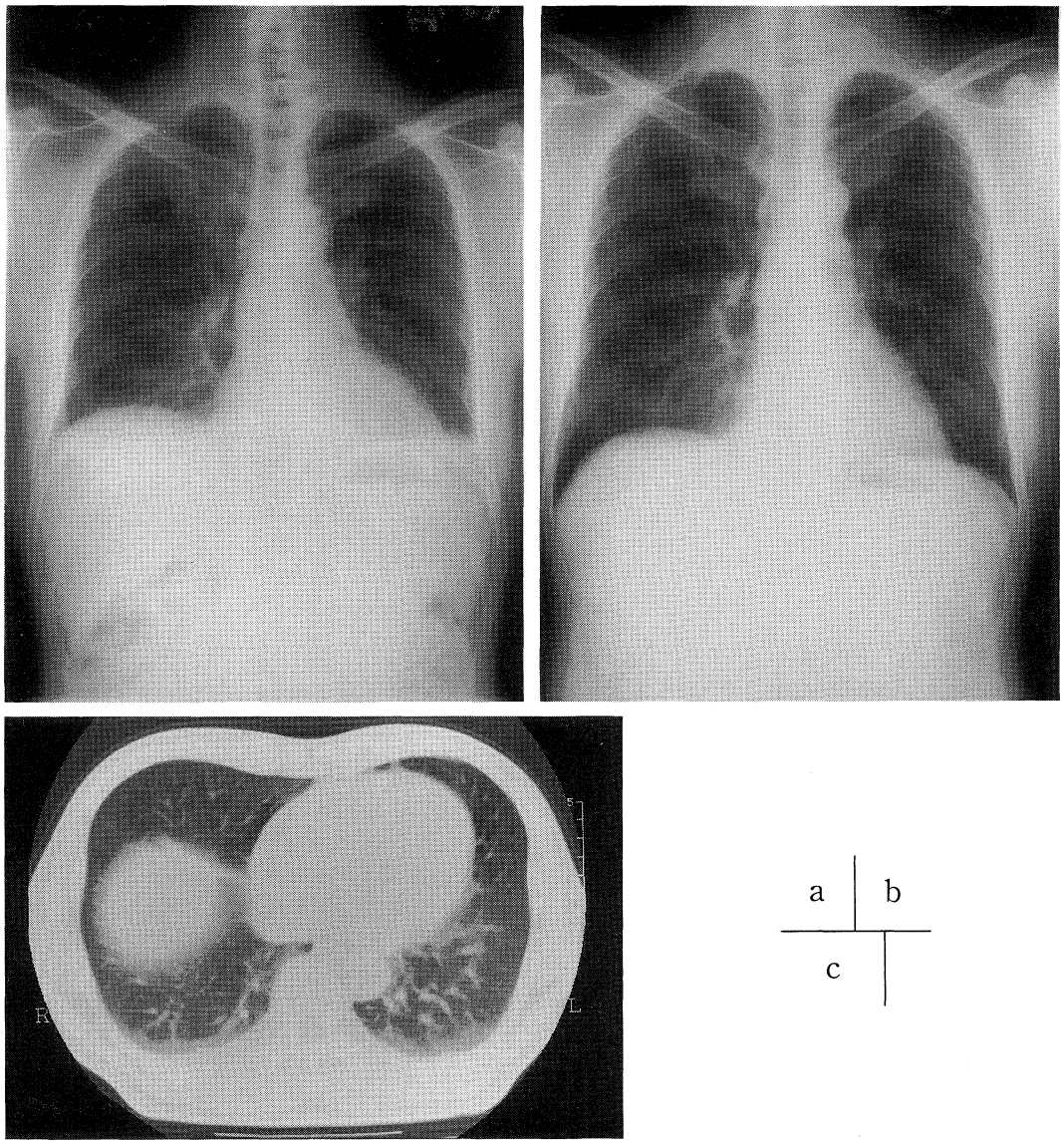


**Figure 1. Chest roentgenogram (a) and chest CT on admission (c) revealed an interstitial shadow. Chest roentgenogram 2 days after admission (b), abnormal shadow was nearly diminished.**

0.8% eosinophils, 13.2% neutrophils, 19.6% lymphocytes, and an absolute total cell count of $2 \times 10^5$ cells/ml. CD4/8 ratio of BAL fluid lymphocytes was 0.24. A transbronchial lung biopsy specimen from the right $S^8$ showed moderate lymphocyte infiltration in the alveolar septum, with no granuloma and no organizing exudate in the alveolar space (Fig. 2), the histological findings were consistent with a diagnosis of interstitial pneumonia. The lymphocyte stimulation tests with both drugs were positive and the six constituents of Saikokeisikankyou-tou showed positive results (Table 1). Skin test was also positive to Lycium Halimifolium Mil and the six constituents of Saikokeisikankyou-tou (Table 1). Under informed consent upon complete explanation, the patient was challenged with both Saikokeisikankyou-tou and Lycium Halimifolium Mil of drugs (Fig. 3). He was challenged with the single usual dose of Lycium Halimifolium Mil. Although he developed no symptoms, peripheral blood eosinophils increased to 12.5% and the CRP level in the serum became slightly elevated. These findings suggest that it was unlikely that Lycium Halimifolium Mil was the cause of pneumonitis. At 21 days following presentation, he was challenged with a single typical dose of Saikokeisikankyou-tou. Ten hours later, he developed shortness of breath and high fever. The following day, chest roentgenogram revealed infiltration in the left lower lung field. CRP was elevated to 7.2 mg/dl and the white blood cell count (WBC) increased to 17,600/μl. The challenge test with Saikokeisikankyou-tou strongly supported the diagnosis of drug-induced pneumonia. Steroid therapy was not indicated and his pneumonia improved by discontinuance of both drugs.

## Discussion

Since Tsukiyama et al (1) reported the first case of pneumonitis induced by Shousaiko-tou in 1989, several cases of herbal drug-induced pneumonitis have been reported, most of which were caused by Shousaiko-tou. Although the pathogenesis of drug-induced pneumonitis is not completely understood, intolerance to side effects, secondary effect and idiosyncrasy allergic reaction are thought to be the most important factors (2). Allergic pneumonitis is not related to the total cumulative dosage and it tends to occur seven to ten days after exposure (3). Allergic pneumonitis is particularly mediated via type III and IV allergic reaction (4). The present case was considered to be caused by both type I allergic reactions based on the positive skin test and also type IV allergy based on the lymphocyte

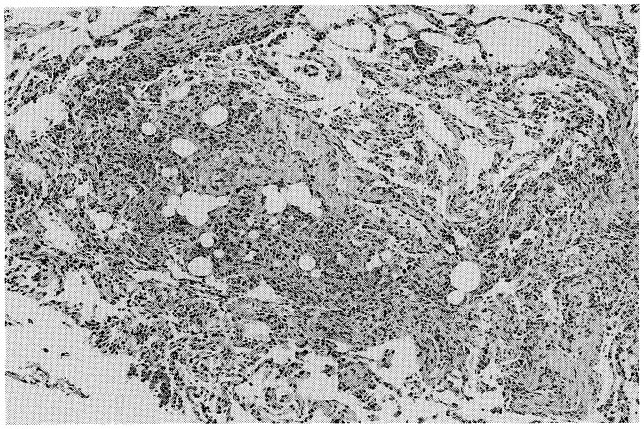

**Figure 2. A transbronchial lung biopsy specimen from the right $S^8$ showing moderate lymphocyte infiltration in the alveolar septum, with no granuloma and no organizing exudate in the alveolar space (HE stain, ×40).**

**Table 1. Immunological Results**

| | DLST* | Skin test (flare, $mm^2$) | |
|---|---|---|---|
| | Stimulation index | Early | Delayed |
| Control | 1.8 | 0 × 0 | 0 × 0 |
| Kukiko | 3.5 (+) | 28 × 30 | 15 × 15 |
| Saikokeisikankyou-tou | 3.2 (+) | NT | NT |
| Kanzou | 2.2 (+) | 40 × 43 | 20 × 21 |
| Kankyou | 5.3 (+) | 15 × 15 | 25 × 30 |
| Borei | 1.3 (–) | 0 × 0 | 0 × 0 |
| Ougon | 18.1 (+) | 38 × 40 | 12 × 15 |
| Keisi | 3.6 (+) | 10 × 14 | 15 × 15 |
| Karokon | 2.6 (+) | 5 × 5 | 10 × 11 |
| Saiko | 2.5 (+) | 18 × 22 | 25 × 30 |

*Drug lymphocyte stimulation test; NT: not tested.

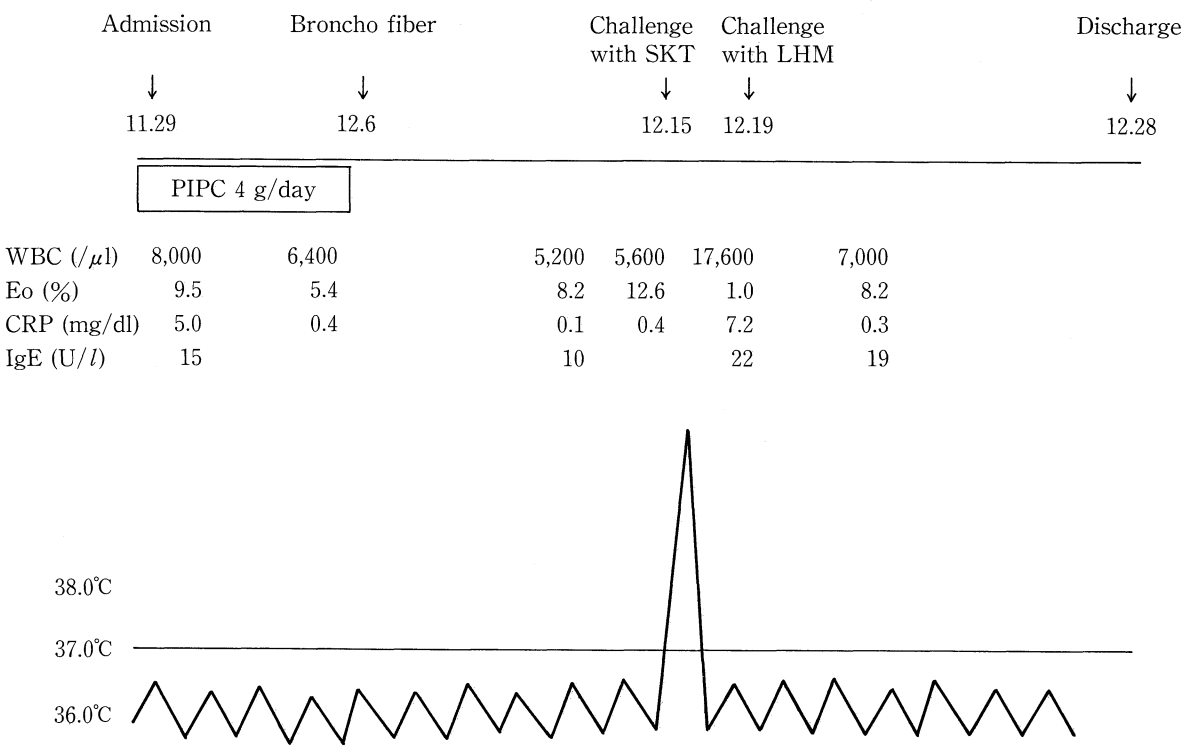


**Figure 3. Clinical course including oral challenge test with Licium Halimifolium Mil or Saikokeisikankyou-tou. SKT: Saikokeisikankyou-tou, LHM: Licium Halimifolium Mil.**

stimulation test.

The three constituents of Saikokeisikankyou-tou (Saiko, Ougon and Kanzou) are also included in Shousaiko-tou. Among them, Ougon is thought to be the most important cause of pneumonitis because of previously reported highly positive lymphocyte stimulation tests (5). Recently, it has been postulated that BAL is useful for the diagnosis of drug-induced pneumonitis. Akoun et al (6) and Rosenow et al (7) reported that patients with drug-induced pneumonitis show an increased number of lymphocyte in BAL fluid. The lymphocyte differential in BAL fluid was slightly increased in the present case, and the CD4/8 ratio was low as in the reported cases. These findings support the diagnosis of drug-induced pneumonitis in the present case. A common pathologic finding of drug-induced pneumonitis has been described as eosinophilic pneumonia which is characterized by infiltration of lymphocytes and eosinophils in alveolar septum, fibrosis and organizing exudate in air space. Cooper et al (8) described that drug-induced pneumonitis can be classified as chronic interstitial pneumonia, diffuse alveolar damage, bronchitis obliterans organising pneumonia (BOOP), and eosinophilic pneumonia.

Recently, pneumonitis induced by Shosaiko-tou is often reported. Kanzou, Saiko, and Ougon, its constituents, are known to inhibit release of chemical mediators (9). Saikokeisikankyou-tou is reported to be effective for treatment of rheumatoid lung (10). As herbal drugs have both benefit and disadvantages (11), it is important to be careful in its use.

We described the first case of pneumonitis induced by Saikokeisikankyou-tou diagnosed by positive lymphocyte stimulation test, skin test and challenge test. This report highlights the importance of careful evaluation of exposure in patients presenting with non-specific pneumonitis or atypical pneumonia.

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