Sai-rei-to-induced Lung Injury: A Case Report and Brief Review of the Literature

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Abstract

An 81-year-old man was admitted to our hospital due to persistent fever and dyspnea with pulmonary infiltrates. He was treated successfully by discontinuing his current medications, including Sai-rei-to, and administering glucocorticoids. Drug lymphocyte stimulation tests showed a positive result for Sai-rei-to alone, and the resumption of other regular drugs did not re-induce the lung injury. Therefore, we diagnosed the patient with Sai-rei-to-induced lung injury. Sai-rei-to is a combination drug that consists of Sho-saiko-to and Gorei-san. This paper briefly reviews drug-induced lung injury caused by Sai-rei-to or its components with a case report.

Key words: Chinese herbal medicine, drug-induced lung injury, Sai-rei-to, Sho-saiko-to

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Introduction

The occurrence of lung injury caused by Chinese herbal medicine was first reported in 1989 (1). Sho-saiko-to (Xiao-chui-hu-tang) is the most common herb that contributes to the risk of suffering from drug-induced lung injury (2). Sai-rei-to is a combination drug that consists of Sho-saiko-to and Gorei-san (Wu-ling-san) and contains twelve crude drugs. Although several cases of Sai-rei-to-induced lung injury have been previously reported (3-12), no reports discussing each constitutive crude drug have so far been completed. Concerning the aforementioned case, we diagnosed the patient with Sai-rei-to-induced pneumonitis and examined drug sensitivity using drug lymphocyte stimulation tests (DLST) for each crude drug. The aim of this report was to highlight a case of lung injury caused by Sai-rei-to and to briefly review the literature pertaining to Sai-rei-to and Sho-saiko-to.

Case Report

Since August 2011, an 81-year-old Japanese man had regularly undergone transurethral resection of a recurring tumor localized in his bladder. The patient began to complain of a dry cough and fever ten days after starting treatment with Sai-rei-to to prevent urethral stricture. The symptoms became progressively more severe, and he therefore visited our hospital in May 2012. He was an ex-smoker (Brinkman index: 80), had been exposed to neither dust nor pet animals, including birds, and had not been found to have any lung diseases.

A physical examination performed on admission revealed a body temperature of 39.2°C, a percutaneous oxygen saturation of 90% on 4 L/min of oxygen, a respiratory rate of 22 breaths/min, a blood pressure of 125/91 mmHg and a heart rate of 90 beats/min. No bilateral crackles were detected on chest auscultation. The laboratory findings revealed a normal leukocyte count (8,690/ μ L) without eosinophilia, the presence of lactate dehydrogenase (213 IU/L) and

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Figure 1. Chest radiograph obtained on admission showed diffuse ground-glass attenuation (a). This finding worsened with bilateral pleural effusions five days after admission (b), then improved two months and 17 days after the withdrawal of Sai-rei-to and treatment with glucocorticoids (c).

Figure 2. Computed tomographic scans of the chest showed diffuse ground-glass attenuation and thickening of the bronchovascular bundles with small bilateral pleural effusions on admission (a) and a left-sided dominant expansion of ground-glass attenuation five days after admission (b).

KL-6 [228 U/mL in an electrochemiluminescence immunoassay (ECLIA) performed using the Picolumi KL-6 kit (Eidia, Tokyo, Japan)] and elevated serum levels of C-reactive protein (9.15 mg/dL). An arterial blood gas analysis performed with the patient on 4 L/min of oxygen indicated respiratory alkalosis (pH: 7.051, PaO₂: 53.8 Torr, PaCO₂: 26.0 Torr, HCO₃⁻: 20.4 mmol/L). Tests for antinuclear antibodies and other various autoantibodies in the serum were negative. A sample of the patient's sputum was not available due to his non-productive cough. A chest radiograph taken on admission is shown in Fig. 1a, which demonstrates bilateral diffuse ground-glass attenuation. High-resolution com-

puted tomography (HRCT) (Fig. 2a) demonstrated bilateral ground-glass attenuation, thickening of the bronchovascular bundles and a small amount of right-sided pleural effusion; however, neither honeycomb lesions nor emphysematous changes were observed.

Initially, the patient was treated with 13.5 g/day of intravenous piperacillin/tazobactam and 500 mg/day of intravenous azithromycin because he was suspected of having community-acquired pneumonia, including pneumonia caused by atypical pathogens. However, his symptoms did not improve and in fact gradually worsened. He was then suspected to have drug-induced lung injury, and all of his

Table. Clinical Characteristics of Sai-rei-to-induced Lung Injury

case	age gender	Duration of medication	WBC /μL	CRP mg/dL	LDH IU/L	KL-6 U/mL	CT findings	DLST
Yamawaki [3]	74 M	110	9,840	23.0	703	ND	GGA, consolidation	Negative
Yamawaki [4]	66 F	23	10,030	14.4	750	ND	Reticular opacities	Positive
Maeno [5]	51 F	90	5,030	<0.3	481	ND	GGA, Atelectasis	Negative
Shinohara [6]	61 M	45	9,180	3.0	592	ND	GGA	Positive
Arimoto [7]	54 M	About 30	7,400	5.05	814	ND	GGA	Positive
Sakamoto [8]	68 M	8	9,600	11.1	936	ND	GGA, consolidation	Negative
Sakamoto [8]	52 M	49	11,400	17.7	1,037	1,120	GGA	ND
Itoh [9]	77 M	16	13,130	3.71	722	364	GGA	Positive
Takayama [10]	65 F	About 90	8,000	6.7	431	515	GGA	Positive
Narita [11]	83 F	8	7,200	10.6	560	425	GGA	Negative
Miyagawa [12]	38 M	About 40	12,600	1.67	430	849	GGA, consolidation	Positive
Present	81 M	14	8,690	9	213	228	GGA	Positive

Abbreviation: CRP: C-reactive protein, CT: computed tomography, DLST: drug lymphocyte stimulation test, GGA: ground-glass attenuation, LDH: lactate dehydrogenase, ND: no data, WBC: white blood cell

current oral medications, including Sai-rei-to, telmisartan and allopurinol, were discontinued three days after hospital admission. At that time, 14 days had passed since he had begun taking Sai-rei-to. Although his fever decreased slightly, the patient's respiratory status and radiological findings did not improve (Figs. 1b, 2b). Therefore, he received steroid pulse therapy (1,000 mg/day of methylprednisolone for three days) for severe respiratory distress five days after admission. His fever and dyspnea rapidly improved within several hours after the first infusion of methylprednisolone, and the infiltrates observed on chest radiograph gradually diminished (Fig. 1c). The patient received maintenance therapy, including low-dose oral prednisolone, which was slowly reduced over three weeks. DLST conducted 34 days after the withdrawal of prednisolone demonstrated a positive result for Sai-rei-to and negative results for telmisartan and allopurinol. Regarding the twelve crude drugs contained in Sai-rei-to, DLST indicated positive results for bupleurum root, scutellaria root and licorice, as the components of Sho-saiko-to, and umbrella polypore, which is a component of Gorei-san. To date, no relapse has occurred, even though the patient resumed taking his regular medications, excluding Sai-rei-to.

Discussion

There is no 'gold standard' for the diagnosis of drug-induced lung injury, and the condition is clinically diagnosed based on the time course and a detailed history of medication use (13). In the present case, the patient had received Sai-rei-to for two weeks prior to visiting the hospital. His symptoms and radiological findings were reversible following the withdrawal of his regular drugs and the admin-

istration of steroid therapy. The resumption of his regular medications, excluding Sai-rei-to, did not induce any recurrence of lung injury, and DLST for Sai-rei-to indicated a positive result. Therefore, we diagnosed the patient with Sai-rei-to-induced lung injury. However, we could not note the type of inflammatory cells in the patient's lungs because histopathological examinations were not performed. Considering the serum KL-6 level in this case was within the normal range on admission, there may be a possibility of an allergic reaction that was not typical of lung injury. In addition, chest CT performed five days after admission revealed an increased right-dominant pleural effusion. This phenomenon suggests the possibility of congestion. Two main diagnostic criteria include drug provocation tests (14, 15). However, both are considered to be ethically unacceptable. This case met the criteria, except for a drug provocation test.

Articles regarding the eleven cases of Sai-rei-to-induced lung injury are available on MEDLINE and the Japanese articles database, including ICHUSHI (Table) (3-12); however, they are primarily written in Japanese only, with the exception of two case reports written in English (8). According to these reports, including the one in hand, one of 12 patients is deceased, and the average period from the initiation of the drugs to the onset of lung injury is 35 (range 8-110) days. This period has a tendency to vary depending on the type of drug administered, and it may take approximately two months for symptoms to surface after the start of Chinese herbal medicine (2). Sai-rei-to is a combination drug that consists of Sho-saiko-to and Gorei-san; thus, the characteristics of each drug should be reviewed.

Sho-saiko-to is the most common Chinese medicine reported to cause drug-induced lung injury. The first case of Sho-saiko-to-induced lung injury was reported in 1989 (1).

Since evidence for hepatocellular chemoprevention with Sho-saiko-to was reported (16), the number of patients treated with Sho-saiko-to has increased (12, 17, 18). Additionally, in a study by Sato and coauthors of the characteristics of 72 patients with Sho-saiko-to-induced lung injury reported between 1990 and 1996 in Japan, eight patients were found to have died of lung injury. There are also significant differences between survival and non-survival groups concerning the period from the onset of symptoms to withdrawal of the drugs (5.8 ± 7.4 days vs. 16.8 ± 14.8 days), but not in the period from initiation of the drugs to the onset of symptoms (51.0 ± 43.6 days vs. 42.2 ± 21.4 days) (2). These results highlight the importance of early detection. Patients with underlying lung diseases such as idiopathic pulmonary fibrosis have worse prognoses than those without underlying lung diseases (2). This indicates that Sho-saiko-to-induced lung injury is caused not only by an allergic mechanism, but also by direct effects. Suganuma and coauthors reported that Sho-saiko-to enhances cytokine release from lung fibroblasts *in vitro* and noted that the effects were more noticeable in fibroblasts obtained from idiopathic pulmonary fibrotic lungs than in those obtained from healthy lungs (19).

Sho-saiko-to contains seven crude drugs. Among them, bupleurum root and scutellaria root are thought to be potential causes of lung injury. Many Chinese herbal medicines contain both drugs, and some can induce lung injury in a similar way to Sho-saiko-to (20, 21). It remains to be elucidated whether one or both drugs effect the lungs. The aforementioned case involved positive results from DLST for both drugs. Although the present patient showed a positive result for licorice, licorice-induced lung injury is very rare (21). It is therefore reasonable to regard our case as a case of drug-induced lung injury caused by bupleurum root and scutellaria root. As many researchers have pointed out, DLST is not particularly accurate, and the test itself has many clinical and immunological problems (22-25). A strong emphasis must be placed on the patient's clinical course rather than the results from DLST because it is too risky to accept the results without thorough questioning. As shown in Table, there are no differences in patient backgrounds between cases that are positive or negative for DLST. In addition, the diagnostic accuracy of DLST, including the cutoff value for drug-induced lung injury, has not been fully evaluated, and further large prospective studies are needed. According to a case series based on adverse drug reaction reporting, 63.9% of Sho-saiko-to-induced lung injury cases were diagnosed based only on the patient's clinical course, 26.4% were diagnosed based on the patient's clinical course and the results of DLST and 9.7% were diagnosed based on drug provocation tests (2). Approximately half of the cases showed positive results of DLST for Sho-saiko-to. So far, as the practicality of DLST cannot be completely denied, it is necessary to survey objectively using large case series for each drug.

In contrast, neither Gorei-san nor umbrella polypore have been reported to induce lung injury, and, as such, the pres-

ent case seems to involve lung injury caused by Sho-saiko-to, although the influence of drug interactions among these crude drugs cannot be ruled out completely.

Drug-induced lung injury is treated using withdrawal of the causative medications and administration of glucocorticoids as needed. Among patients with Sho-saiko-to-induced lung injury, 10.9% are cured following withdrawal of medication only, while the remaining patients require glucocorticoid administration (2). There should be no hesitation in administering glucocorticoids if patients do not improve following withdrawal of drugs alone because the mechanism of Sho-saiko-to-induced lung injury may consist of both direct and allergic effects. Regarding the present case, the patient received glucocorticoids because his condition did not adequately improve following withdrawal of medications alone. Administration of steroids enables patients to recover without developing sequelae.

We reviewed drug-induced lung injury caused by Sai-rei-to and Sho-saiko-to and their components. A warning exists concerning the adverse effects of common drugs that have enormous significance in the medical services community; however, Chinese herbal medicine is not necessarily associated with a higher incidence of adverse effects (26). It is therefore considered to be of clinical importance to note that any drug can induce lung injury. However, an overhaul regarding the appropriateness of medications is required. Antitumor necrotizing factor alpha can improve interstitial pneumonitis and has the opposite effect on drug-induced lung injury (27). Similarly, bupleurum has also received attention for its antifibrotic effects (28). We must remain conscious of whether using these medications is really necessary to improve patient conditions and must quickly detect the adverse effects of such medications.

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

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