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【 CASE REPORT 】

Pneumonitis Due to *Oren-gedoku-to* (Coptis Detoxifying Decoction)

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Abstract:

A 54-year-old man started to take *oren-gedoku-to* (coptis detoxifying decoction) because he was experiencing chronic hot flashes, night sweats and insomnia. He developed a high fever from the day of intake. At day 17, he stopped taking *oren-gedoku-to* because of malaise and chills, and he was admitted to our hospital. Drug-induced pneumonitis was suspected, and all drugs were stopped. Consequently, his symptoms, laboratory data and chest X-ray findings markedly improved. The results of a lymphocyte stimulation test were positive for *oren-gedoku-to* and one of its components, *ougon* (Baikal skullcap). Based on these findings, we diagnosed him with pneumonitis caused by *ougon*.

Key words: *oren-gedoku-to*, *Ougon*, lymphocyte stimulation test, drug-induced pneumonitis

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Introduction

We encountered a case of drug-induced pneumonitis caused by *oren-gedoku-to* (coptis detoxifying decoction), which is an extract from bitter-tasting roots, bark and fruits containing *oren* (Japanese golden thread), *ougon* (Baikal skullcap), *oubaku* (Amur Cork tree) and *sanshishi* (Cape jasmine).

Doctors in Japan are familiar with treatments that use Japanese herbal medicine (JHM), a form of Oriental medicine. However, there are around 40 reports of JHM-induced pneumonitis per year in Japan. The number of cases has increased since *sho-saiko-to* (minor bupleurum decoction)-induced pneumonitis was first reported in 1989 (1). All JHMs comprise several crude drugs, many of which contain *ougon* and *kanzo* (liquorice). *Ougon* has been suspected to be the cause of this pneumonitis, since the drug-induced lymphocyte-stimulating test (DLST) was positive (2), whereas *kanzo* is well known to cause pseudohyperaldosteronism.

The diagnosis of drug-induced pneumonitis is often difficult, and clinical evidence needs to be accumulated from suspected cases (3). The pharmacological mechanisms underlying JHM are not well understood, and it is therefore important to check the history of each medication and obtain detailed information on each drug's use. However, there are few articles in English on JHM-induced pneumonitis because, thus far, Japanese cases have only been reported in the Japanese literature. This needs to change; it is important to submit reports in English in order to gain wider knowledge and identify new strategies for the treatment of JHM-induced pneumonitis.

Case Report

A 54-year-old Japanese man started to take *oren-gedoku-to*, a type of JHM, because it had been prescribed by a local clinic on Day 1 for the hot flashes he had been experiencing for 2 years. He developed a high fever and chills after taking *oren-gedoku-to* for 17 days. After developing dyspnea mainly when exercising, he decided to stop taking the medication on Day 17. A few weeks later he was admitted to his local clinic with symptoms of dyspnea on exercise, malaise

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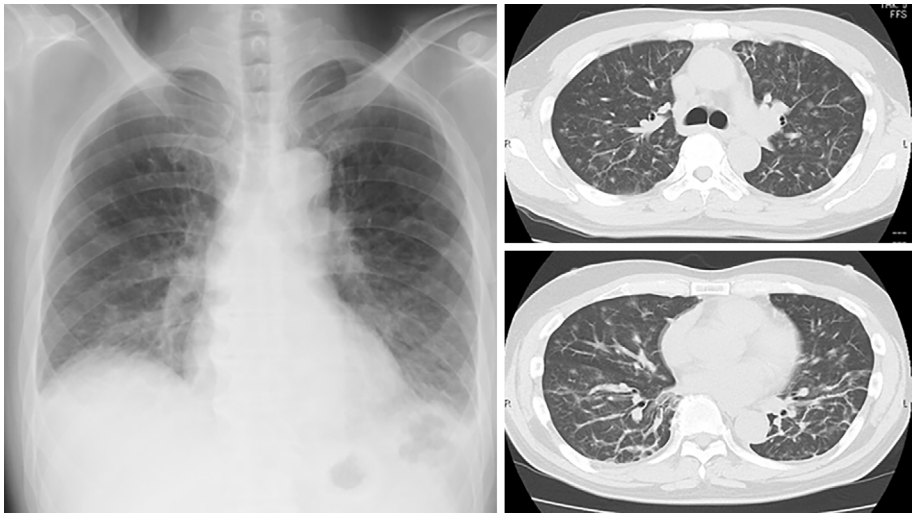


Figure 1. **Left: Chest X-ray on admission showed a diffuse reticular appearance particularly in both lower lung fields. Right: Chest CT revealed diffuse small patchy shadows and trabecular shadows in both lower lung fields.**

and chills. When admitted to our hospital on Day 21, he was afebrile, and slight fine crackles were heard in his lower back.

Chest X-ray showed interstitial shadows in both lower lung fields, and computed tomography (CT) showed diffuse patchy and funicular opacities and volume loss predominantly in both lower lung areas (Fig. 1). Peripheral leukocyte and eosinophil counts were 6,500 cells/μL and 436 cells/μL, respectively, and the serum C-reactive protein level was 2.31 mg/dL. The hepatic transaminase levels (AST 41 U/L, ALT 39 U/L) were mildly elevated with slight elevation of the lactate dehydrogenase level (267 U/L), and KL-6 was within the normal ranges but SP-D was elevated (Table 1). The SpO_2 was low at around 85% after minor exertion. Restrictive impairment and decreased single-breath diffusing capacity for carbon monoxide were demonstrated by pulmonary function tests. Lymphocytes and eosinophils were dominant (73.6% and 12.6% respectively), and the CD4/CD 8+T-cell ratio was low in the bronchoalveolar lavage fluid (BALF) obtained on Day 25 (Table 1). Many alveolar macrophages existed, and mild lymphocytic interstitial inflammation was seen in the transbronchial lung biopsy (TBLB) specimens taken from the right middle and lower lungs (Fig. 2).

Although antibiotics and steroids were not administered, malaise, cough, hypoxemia and interstitial shadows gradually decreased up to Day 33. The patient was discharged from hospital on Day 43; the total hospitalization duration was 23 days (Fig. 3). We suspected that the patient had developed hypersensitivity pneumonitis from the Japanese summer, but he had no remarkable inhalation history, and there were no reports of deterioration in his housing conditions. After the patient stopped taking *oren-gedoku-to*, his fever and respiratory symptoms did not recur. Because lymphocytes obtained from the peripheral blood were positive in the DLST for *oren-gedoku-to*, we diagnosed him as having *oren-gedoku-to*-induced pneumonitis.

The JHM *oren-gedoku-to*, which is a mixture of four crude drugs-oren, *ougon*, *oubaku* and *sanshishi*-is often prescribed for hot flashes. We therefore next performed a DLST for each component, and only *ougon* was positive, resulting in a final diagnosis of *ougon*-induced pneumonitis (Table 2). His symptoms as well as radiograph findings and oxygenation recovered almost completely, and his peripheral eosinophil count returned to normal. Pulmonary function test findings also returned to normal, and his single-breath diffusing capacity for carbon monoxide recovered by Day 56 without using steroids or other anti-inflammatory drugs (Fig. 3).

Discussion

Tsukiyama et al. reported the first case of JHM *sho-saiko-to*-induced pneumonitis in Japan in 1989 (1). In 1996, the Japanese Ministry of Health and Welfare issued letters regarding fatal cases of interstitial pneumonia potentially attributable to *sho-saiko-to* (4). We experienced a case of *oren-gedoku-to*-induced pneumonitis. The number of reports of cases involving *sho-saiko-to* and *sairei-to* (minor bupleurum decoction plus poria powder with five herbs) was around 40% (3). However, *oren-gedoku-to*-induced pneumonitis was reported by only one author (3).

Ougon and *kanzo* appear to be commonly contained in causative JHMs (3). *Oren-gedoku-to* is made up of four components, including *ougon*. Only one previous report on *oren-gedoku-to* by Nishimori et al. (5) indicated the cause of pneumonitis as being *ougon*. They carried out a provocation test for *sho-saiko-to* and *oren-gedoku-to* because the DLST was negative for each drug (5). They concluded that *ougon* was the cause of pneumonitis in their patient because *ougon* was the common component in these drugs (5). *Ougon* is well-known as a causative crude drug for JHM-induced

Table 1. Laboratory Findings.

Hematology				
WBC	6,500 /mm^3	Serology		
Neu	56.5 %	CRP	2.31 mg/dL	
Lym	30.2 %	HBs antigen	negative	
Mono	6.1 %	HCV antibody	negative	
Eos	6.7 %	HIV antibody	negative	
Baso	0.5 %	C. pneumoniae antibody	negative	
RBC	488×10^4 /mm^3	ANA	<×40	
Hb	14.4 g/dL	PR3-ANCA	<2.0 IU/mL	
Ht	43.5 %	MPO-ANCA	<3.5 IU/mL	
Plt	34.2×10^4 /mm^3			
		Bronchoalveolar lavage fluid		
Biochemistry		Total cell counts	19×10^4 /mL	
TP	7.1 g/dL	Macrophages	10.8 %	
Alb	3.8 g/dL	Lymphocytes	73.6 %	
BUN	11.0 mg/dL	Neutrophils	3.0 %	
Cre	0.93 mg/dL	Eosinophils	12.6 %	
LDH	267 U/L			
AST	41 U/L	Lymphocyte subset		
ALT	39 U/L	CD3	91 %	(54.3-81.9)
γ-GTP	98 U/L	CD4	8.3 %	(24.3-49.7)
ALP	397 U/L	CD8	76.3 %	(18.4-49.0)
T-Bil	0.6 mg/dL	CD4/CD8 ratio	0.1	(0.4-1.9)
KL-6	219 U/mL			
SP-D	211.5 ng/mL			

WBC: white blood cell count, Neu: neutrophil, Lym: lymphocyte, Mono: monocyte, Eos: eosinophil, Baso: basophil, RBC: red blood cell count, Hb: hemoglobin, Plt: platelet, TP: total protein, Alb: albumin, LDH: lactate delydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, T-Bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine, KL-6: Sialylated carbohydrate antigen Krebs von den Lungen-6, SP-D: surfactant protein-D, CRP: C reacting protein, ANA: anti-nuclear antibody, PR3-ANCA: proteinase3-anti-neutrophil cytoplasmic antibody, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibody, C. pneumoniae: Chlamydophila pneumoniae

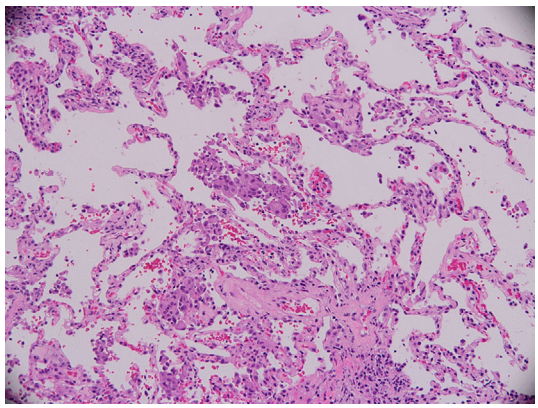
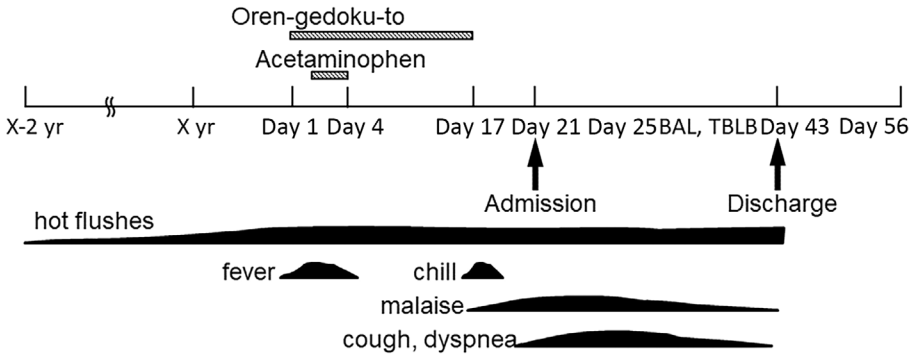


Figure 2. Histology of transbronchial lung biopsy specimen: Alveolar tissue with macrophage aggregation and interstitial tissue with mild lymphocytic infiltration were recognized (Hematoxylin and Eosin staining, ×400).

pneumonitis.

Since the DLST reportedly has a median positive rate of 67.6% for patients with JHM-induced pneumonia (6), we know that it is not a completely reliable test; however, there is no other commercial test available that can analyze the causal material for drug-induced pneumonitis. Enomoto et al. reviewed 73 patients with JHM-induced pneumonitis and found that most pneumonitis events occurred within three months of JHM initiation (3). Furthermore, their research revealed that DLSTs using serum samples does not give sufficiently high positive rates (3). Some researchers also reported that the sensitivity of the DLST is low (7), and that it is better to use BALF than peripheral blood as samples (8). Whether serum or BALF is better for use as a sample for the DLST needs to be examined in greater detail.

The Japanese Ministry of Health, Labour and Welfare has approved 294 JHMs as of 2018. *Ougon* is suspected to cause JHM-induced pneumonitis in many cases, and we found that 27 JHMs produced by Tsumura contained *ougon*. The results of a DLST using peripheral blood were positive for *ougon*, although the sensitivity of the DLST was not enough to detect drug-induced pneumonitis (9). In addition, the activity of each crude drug may change after being mixed with other drugs. The reliability of the DLST results for JHMs is controversial because they are generally contaminated with non-specific mitogens from plants (2). How-



Eos (cells/μL)	436	348	194	262
Pulmonary function test				
VC			2.82L	4.70L
%VC			64.80%	108.00%
$FEV_{1.0}$			2.15L	3.40L
$FEV_{1.0\%}$			76.24%	72.34%
%DLCO			58.60%	88.90%

Figure 3. Clinical course as well as findings from pulmonary function tests and the number of eosinophils in the peripheral blood. Eos: Eosinophils, VC: vital capacity, %VC: percent vital capacity, $FEV_{1.0}$: forced expiratory volume in one second, $FEV_{1.0\%}$: forced expiratory volume in one second/ forced vital capacity, %DLCO: percent single-breath diffusing capacity of the lung for carbon monoxide

Table 2. Results of Drug-induced Lymphocyte Stimulation Test.

Drug	S.I. (%)	
Oren-gedoku-to (coptis detoxificating decoction)	3.8	(+)
Ingredient	S.I. (%)	
Oren (Japanese golden thread)	0.9	(-)
Ougon (Baikal skullcap)	7.2	(+)
Oubaku (Amur Cork tree)	1.2	(-)
Sanshishi (Cape jasmine)	1.4	(-)

ever, since a provocation test exerts undue stress on most patients, we usually perform a DLST as the first step; we should therefore consider the reliability of the results in every case.

Our patient recovered from pneumonitis soon after stopping taking *oren-gedoku-to* and without using steroids, suggesting that the severity of adverse effects might depend on how long the causative drugs are taken for. We also suspected that pneumonitis with elevated SP-D, but not KL-6, was likely to be cured with or without steroids because it was suggested that KL-6 rather than SP-D might be involved in pulmonary fibrosis (10).

Although many different types of interstitial lung disease are involved in pneumonitis caused by JHMs, previous reports on JHM-induced pneumonitis have demonstrated various features, including diffuse interstitial inflammatory changes on CT scans, restrictive ventilatory impairment on pulmonary function tests, lymphocytic alveolitis on transbronchial lung biopsies (TBLBs), and lymphocytosis with a predominance of the CD8+T cell subset in BALF (2). We should be aware that each ingredient in a JHM can cause pneumonitis through certain biological pathways.

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

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