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【 CASE REPORT 】

Two Cases and a Review of the Literature Regarding Severe Interstitial Lung Disease Induced by Hangeshashinto

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Abstract:
Hangeshashinto is a traditional Japanese herbal medicine that is widely recognized for its efficacy in relieving mucositis induced by chemotherapy and radiotherapy. We herein present the cases of two patients with head and neck cancer who were clinically diagnosed with severe drug-induced interstitial lung disease (DILD) following Hangeshashinto administration for radiation-induced mucositis. Although Hangeshashinto has beneficial properties, it is also associated with a relatively low incidence of DILD, including some reports of death. To ensure patient safety, greater attention should be paid when prescribing Hangeshashinto, especially for elderly patients with factors predisposing them to develop severe DILD.

Key words: Hangeshashinto, Kampo medicine, drug-induced interstitial lung disease, mucositis, radiation therapy

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Introduction

Hangeshashinto is a Kampo medicine used for stomatitis, diarrhea, indigestion, and nausea. A wealth of efficacy data on Hangeshashinto have been reported from basic, animal, and human clinical investigations of mucositis resulting from cancer therapy, particularly chemotherapy and radiotherapy (1-6). Radiotherapy is the cornerstone treatment for head and neck cancer; however, it often induces severe mucositis in the upper respiratory tract, which can lead to unplanned treatment interruptions and it may adversely affect patient outcomes (7). To mitigate the risk of mucositis, Hangeshashinto was prescribed.

Case Reports

Case 1

An 88-year-old man with tongue cancer (pT3N2bM0) and a history of smoking (Brinkmann Index: 575), hypertension, angina pectoris, atrial fibrillation, and hyperuricemia was found to have local recurrence 7 months after surgery, which was considered medically inoperable considering his advanced age and comorbidities. Salvage treatment consisting of radiotherapy alone (70 Gy in 35 fractions) has been proposed. To mitigate the risk of mucositis, the patient was promptly prescribed (day 1) Hangeshashinto [2.5 g per dose, administered thrice daily; Tsumura (Tokyo, Japan)] based on previous studies supporting the prophylactic use of Hangeshashinto (4, 5). Patients were instructed to hold a solution containing Hangeshashinto in their mouth for 30 s and then either swallow or expectorate it if swallowing was difficult.

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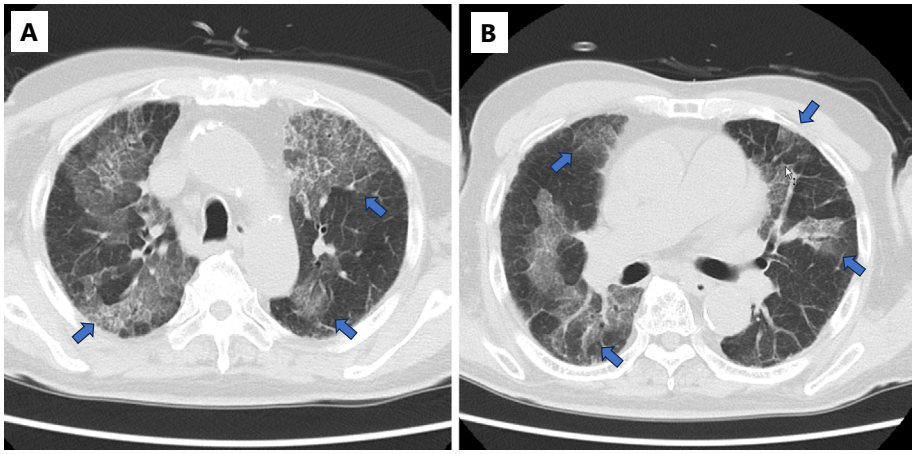

Figure 1. **Axial CT images of the upper (A) and middle (B) lung fields of the Case 1. Multiple non-regional ground-glass opacity was observed in both lungs (arrows).**

Table 1. **Blood Test Findings at Admission of Case 1.**

Hematology		Immune serology		Clinical chemistry	
WBC count	6,900 /μL	CRP	12.83 mg/dL	AST	22 U/L
Leukocyte fractionation		Procalcitonin	0.15 ng/mL	ALT	11 U/L
Neutrophil	86.5 %	KL-6	827 U/mL	LDH	321 U/L
Lymphocyte	5.7 %	B-D glucan	6.7 pg/mL	T-Bil	1.07 mg/dL
Monocyte	6.2 %	Antinuclear antibody	×40	BUN	20 mg/dL
Eosinophil (count)	1.3 % (90/μL)	P-ANCA	(-)	Cre	1.19 mg/dL
Basophil	0.3 %	C-ANCA	(-)	NT-proBNP	2,943 pg/mL

WBC: white blood cell, CRP: C-reactive protein, KL-6: Krebs von den Lungen-6, P-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody, C-ANCA: proteinase 3- antineutrophil cytoplasmic antibody, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, T-Bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine, NT-proBNP: N-terminal pro-brain natriuretic peptide

The patient was then able to swallow the solution. Notably, severe mucositis was not observed; however, at the 32 Gy/16 Fr point (day 26), the patient experienced dyspnea and was promptly transported to the emergency department of our hospital. Physical examination by a respiratory physician revealed clear consciousness, a body temperature (BT) of 36.3°C, blood pressure (BP) of 131/66 mmHg, pulse rate (PR) of 76 bpm, and the saturation of percutaneous oxygen (SpO_2) of 92% on 2 L/min oxygen [PaO_2/FIO_2 (P/F) ratio: 175]. Auscultation revealed bilateral fine crackles in the chest, and chest computed tomography (CT) revealed extensive frosted shadows in both lungs (Fig. 1). Pre-treatment CT showed slight peripheral reticular shadows and traction bronchiectasis in both lungs, suggestive of interstitial pneumonia, but no remarkable changes were observed over the past year. Blood samples showed an inflammatory reaction and elevated levels of Krebs von den Lungen-6 (KL-6) (Table 1). Various specimens submitted to confirm infection yielded negative results.

Differential diagnoses included bacterial pneumonia, atypical pneumonia, drug-induced interstitial lung disease (DILD), and alveolar hemorrhage due to anticoagulation. Given the medication history, CT findings, and elevated KL-6 levels, DILD emerged as the most probable diagnosis. Consequently, the suspected medication, Hangeshashinto, was discontinued immediately (day 26), and steroid pulse therapy with methylprednisolone (mPSL; 1,000 mg/day) for 3 days was initiated (day 29). This was followed by post-therapy with prednisolone (PSL) 30 mg/day for 10 days and the administration of PSL 20 mg/day thereafter.

Unfortunately, there was no noticeable improvement in oxygenation 4 days after pulse therapy (P/F ratio: 85), and the patient opted not to undergo further aggressive treatment (day 33). Two weeks after treatment, there was a slight improvement in oxygenation (P/F ratio: 149), and the chest shadows showed signs of improvement. However, the patient's pulmonary function subsequently deteriorated, and he died 27 days after starting pulse therapy (day 56).

Case 2

An 83-year-old man with a medical history of smoking (Brinkmann Index: 900) and chronic obstructive pulmonary disease (COPD) was diagnosed with supraglottic carcinoma (cT2N0M0). The proposed treatment course involved radiotherapy alone (70 Gy in 35 fractions). In this case, after the initiation of radiotherapy, Hangeshashinto [2.5 g per dose, administered three times daily; Tsumura (Tokyo, Japan)] was prescribed to alleviate grade 2 mucositis, which mani-

Table 2. Blood Test Findings at Admission of Case2

Hematology		Immune serology		Clinical chemistry	
WBC count	7,900 /μL	CRP	11.74 mg/dL	AST	35 U/L
Leukocyte fractionation		Procalcitonin	0.22 ng/mL	ALT	26 U/L
Neutrophil	75.5 %	KL-6	100 U/mL	LDH	235 U/L
Lymphocyte	11.5 %	B-D glucan	5.7 pg/mL	T-Bil	1.12 mg/dL
Monocyte	7.2 %	Antinuclear antibody	×40	BUN	16 mg/dL
Eosinophil (count)	5.7 % (450/μL)	P-ANCA	(-)	Cre	1.17 mg/dL
Basophil	0.1 %	C-ANCA	(-)	BNP	87.8 pg/mL

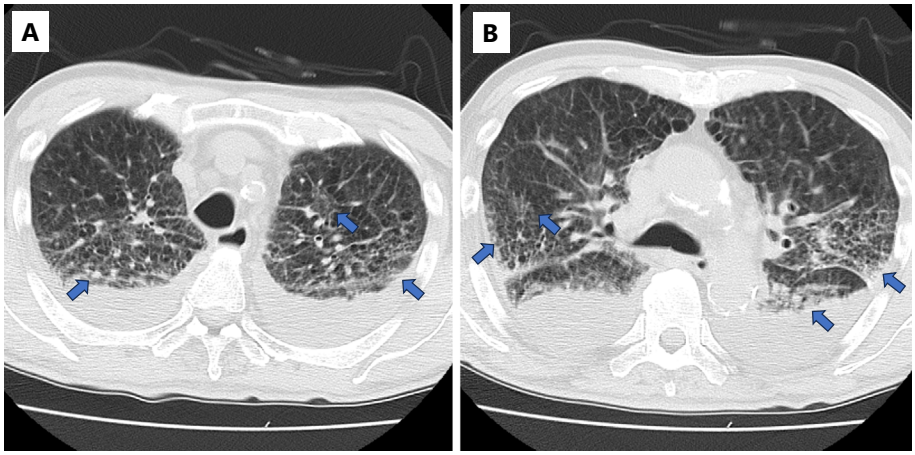

Figure 2. Axial CT images of the upper (A) and middle (B) lung fields of the patient in Case 2. There were bilateral pleural effusions and diffuse thickening of the interlobular septal wall in both lungs (arrows). The lungs also showed the preexistence of background emphysematous changes.

fested at 30 Gy/15 Fr (day 1). No subsequent exacerbation of mucositis was observed. This patient also held a solution containing Hangeshashinto in his mouth for 30 seconds and then swallowed it. At the time of receiving 58 Gy/29 Fr (day 23), the patient developed a fever of 39°C. Due to the ongoing prevalence of COVID-19, he was referred to a specialized outpatient clinic dedicated to febrile patients. Comprehensive blood culture and various tests for infectious diseases yielded negative results. A blood chemistry test revealed no significant findings, except for mildly elevated levels of procalcitonin, eosinophils, and C-reactive protein (Table 2). Nevertheless, given the patient's history of COPD, fever, and decreased oxygenation, pneumonia was suspected, leading to the suspension of radiotherapy and subsequent admission to the hospital for treatment.

Upon admission, the patient presented with clear consciousness: BT was 38.0°C; BP was 160/87 mmHg; PR was 88 bpm; and the SpO_2 89% on room air (P/F ratio:271). He was then referred to a respiratory physician and antibiotic therapy (ceftriaxone 4 g/day for 4 days) was initiated. However, on the sixth day of admission (day 28), chest CT revealed diffuse thickening of the interlobular septal walls in both lungs and bilateral pleural effusions (Fig. 2). Pretreatment CT showed no peripheral reticular shadows in either lung suggestive of interstitial pneumonia. The patient was also found to have a worsening oxygen demand (SpO_2: 91% on 7 L/min oxygen, P/F ratio:87), subsequently requiring intubation. On the same day, considering the possibility of pulmonary edema due to heart failure, blood sampling and echocardiography were performed at the cardiologist's office; however, no abnormalities in his cardiac function were observed. Flexible fiberoptic bronchoscopy was also performed to make a differential diagnosis, and moderate amounts of serum and plasma components were found to be discharged from the bronchi. Bronchoalveolar lavage (BAL) was also attempted, but the amount of fluid obtained was too small to count the cell. As a result, only a culture specimen was submitted. No bacteria, fungi, or viruses that could have caused the pneumonia were identified in the culture specimens. Bacterial pneumonia, atypical pneumonia, DILD, and pulmonary edema due to heart failure were considered in the differential diagnoses. Given the findings of diffuse lung shadows on CT that did not respond to antibiotic therapy, the patient's medication history, and an elevated eosinophil count (450/μL) upon admission, DILD induced by Hangeshashinto was suspected.

Consequently, the suspected medication, Hangeshashinto, was discontinued immediately (day 30), and the patient was prescribed steroid pulse therapy and received mPSL 1,000 mg/day for 3 days starting (day 34), followed by post-therapy with PSL 50 mg/day for 7 days, after which the steroids were tapered off. He showed a rapid improvement in oxygenation (P/F ratios after 3 and 5 days of steroid pulse therapy: 249 and 300, respectively), was extubated 7

Table 3. Characteristics of 98 Cases of Drug-induced Lung Disease Caused by Hangeshashinto.

Sex	
Male	50
Female	48
Age	
Median (range)	70s (10s-90s)
Primary disease	
Cancer	21
Non-cancer	58
Unknown	19
Symptoms	
Diarrhea	18
Stomatitis	12
Reflux esophagitis	8
Other	38
Unknown	22
Period of administration	
Median (range)	30 (4-4,409)
Clinical Outcomes	
Death	7
Recovery	77
Unknown	14

days after the start of pulse therapy (day 40), and was discharged home 48 days after admission (day 70). Radiotherapy was terminated at 58 Gy/29 Fr, and the patient has been under outpatient observation since that time. In the 2 years that have passed since the treatment, no recurrent disease has been noted.

Discussion

Adverse events associated with Hangeshashinto include pseudohyperaldosteronism, myopathy, and DILD, of which DILD can be life-threatening and thus requires extreme caution. Syousaikotou is the Kampo medicine most commonly associated with DILD, whereas cases of DILD caused by Hangeshashinto are rare. To date, only four cases of DILD caused by Hangeshashinto have been reported in Japan, but none have been reported during radiotherapy (8). A search of the adverse drug reaction database maintained by the Pharmaceuticals and Medical Devices Agency in Japan revealed 42 cases of suspected DILD caused by Hangeshashinto during 13 years of available data from 2004 to 2017 (8, 9). In the present study, we re-examined the data from 2004 to 2024 and found a total of 98 cases, indicating that the number of adverse event reports has doubled in the seven years since the previous report (8), and the frequency of such reports has increased. This might be attributable to the increasing frequency of Hangeshashinto prescriptions for mucositis caused by radiation therapy, stomatitis caused by chemotherapy, and cheilitis in dentistry due to reports of its usefulness in these areas (1-6). The details of these 98 cases are listed in Table 3. It was possible to determine the number of fatal cases, primary disease, symptoms, and the duration of administration of Hangeshashinto prior to disease onset, but it was not possible to verify the preexisting pulmonary conditions, chest radiographic abnormalities, or the severity of interstitial lung diseases (ILD).

DILD is generally considered to be caused by cytotoxicity or allergic reactions; however, lung injuries caused by Kampo medicines are considered to be allergy-related. The drug lymphocyte stimulation test is considered safe and is commonly used to identify causative drugs. However, because Kampo medicines contain various compounds other than the active ingredients and may also contain mitogenic substances, such as lectins and mitogens, false-positive test results may be possible. Previous reports suggest that *Scutellariae radix*, a component of Hangeshashinto, is the most likely cause of DILD, but this has not been definitively determined (8).

DILD is estimated to account for only 3-5% of all ILD, and its rarity makes it difficult to distinguish it from other ILDs with respect to its clinical presentation, as well as pathologic and radiologic features (10). In other words, DILD is a diagnosis that excludes other possible causes of pneumonia and it is based on clinical, physiological, and radiologic findings consistent with ILD. Therefore, it is important to check a patient's drug history and rule out other more likely causes, such as infection, pulmonary edema, radiation pneumonitis, and progression of the underlying disease. An internationally recognized treatment-related adverse event severity classification system that is commonly used in clinical trials is the Common Terminology Criteria for Adverse Events, which indicates that the severity of DILD at initial presentation is the most reliable predictor of mortality (11). The mortality rate of DILD is >60%, especially when ventilator management is required (12). Other risk factors for mortality include rapid onset of symptoms, hypoxemia at the time of symptoms, pre-existing ILD, male sex, age >65 years, and a diagnosis of non-small cell lung cancer, which are also associated with higher mortality from DILD (10). The risk factors for the development of DIILD include administration of certain drugs (bleomycin, gemcitabine, epidermal growth factor receptor-targeted agents, mechanistic target of rapamycin protein inhibitors, pemetrexed, leflunomide, methotrexate, amiodarone, and nitrofurantoin), administration of certain drugs to smokers (gemcitabine, epidermal growth factor receptor-targeted drugs, and methotrexate), aging, underlying diseases such as ILD and rheumatoid arthritis, and prior thoracic radiotherapy (10). It is possible that receiving radiation therapy somewhere in the body outside the thoracic region could also trigger DILD. However, although the authors performed a literature search for DILD triggered by non-thoracic radiation therapy, no such evidence or reports were found. In head and neck cancer, radiotherapy to the lung apex should be regarded as a risk factor for DILD; however, in our two cases, the lungs were excluded from the irradiated field, and radiotherapy itself was not considered a risk factor for radia-

tion pneumonitis or DILD. As head and neck cancer is strongly influenced by smoking, smoking-related ILD may be a mortality risk factor for DILD. Evaluation of the lung field by CT was considered to be important to rule out ILD prior to the administration of Hangeshashinto. In Case 1, a patient with recurrent cancer who did not wish to undergo aggressive treatment or invasive examinations, including flexible fiberoptic bronchoscopy, it was difficult to determine whether Hangeshashinto was the true cause of interstitial pneumonia or had a direct role in the patient's death. However, the absence of other plausible explanations for acute severe interstitial pneumonia led us to conclude that Hangeshashinto was the most likely cause of DILD in this case. Pre-treatment CT showed a slight interstitial shadow at the base of the lungs, suggesting the possibility of ILD, but the shadow had not changed for more than one year, we judged that the activity was low, and Hangeshashinto was therefore administered. In Case 2, the patient did not respond to antibiotic therapy, showing diffuse pneumonia with increased eosinophils, but exhibited rapid improvement in respiratory function with steroid pulse therapy; the clinical course was such that DILD with Hangeshashinto was considered as a possible primary diagnosis.

No typical radiologic pattern specific for DILD has been identified, and the concordance between radiologic and pathologic findings is relatively low, thus limiting its usefulness in differential diagnosis (13). However, the CT features of diffuse alveolar damage (DAD) are highly consistent with the histopathological features of DAD, which has been reported to cause high mortality (14, 15). In BAL samples, DILD showed increased lymphocyte, neutrophil, and eosinophil counts and a reversal of the CD4:CD8 lymphocyte ratio; however, these are not specific findings. An important role of BAL testing is to help rule out other causes, especially infections (10). Currently, there are no validated diagnostic or prognostic biomarkers of DILD. However, in a prospective study, the increased KL-6 levels observed in 53% of patients with DILD were correlated with the DAD pattern and more extensive lung involvement and may be a marker for severe cases (16). Although the prompt cessation of the suspected drug and administration of glucocorticoids are commonly used to treat DILD, prospective data are lacking for its efficacy; thus, issues regarding the appropriate dosage of steroids, duration of administration of the drug, and its expected efficacy remain unsettled (10).

Hangeshashinto is effective for treating mucositis caused by various types of cancer. However, caution should be exercised when prescribing Hangeshashinto to patients who are male, elderly, or predisposed to ILD, as this may result in serious DILD. This is the first report of serious DILD in a patient undergoing head and neck radiation therapy. With Hangeshashinto prescriptions during cancer treatment expected to rise further in Japan, we wish to provide this important reminder regarding the potentially life-threatening adverse events associated with its usage. Further research is necessary to gain a deeper understanding of the risk factors associated with the development of DILD following Hangeshashinto use. The identification and investigation of these risk factors will contribute to improved patient selection and the development of appropriate guidelines for the safe and effective use of Hangeshashinto in clinical practice. Additionally, robust studies may help elucidate the underlying mechanisms, patient characteristics, and other factors that may increase susceptibility to DILD when using Hangeshashinto. This knowledge will be invaluable in ensuring patient safety and optimizing the treatment outcomes.

Conclusion

We encountered two cases of severe DILD caused by Hangeshashinto during radiotherapy for head and neck cancer. To ensure patient safety, greater attention should be paid when prescribing Hangeshashinto, particularly for patients with factors that predispose them to develop severe DILD.

Written informed consent was obtained from the participant.

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

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