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# Immunoregulation by Kampo medicines - Clinical application to RA-

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## Introduction

The immunoregulatory effects of Kampo medicines have been reported since the 1970s, and have been analyzed in various diseases since the 1980s to the present. Due to their expected immunoregulatory and biological defense activities, Kampo medicines have been clinically used for chronic hepatitis C,[1,2] influenza infection,[3] allergic diseases,[4,5] autoimmune diseases,[6] malignant tumors,[7,8] and perinatal medicine.[9] Rheumatoid arthritis (RA) is a representative autoimmune disease that has been clinically treated with Kampo medicines.[10] Kampo medicines have played a certain role in the therapeutic strategies for RA.[10] We have clinically used Kampo medicines for RA, and also evaluated their immunoregulatory effects from various aspects. In this study, we discuss part of the clinical effects of Kampo medicines on RA and their immunoregulatory effects while presenting previous results.

## Biological defense

Immunoregulation by Kampo medicines is discussed separately from two aspects, i.e., effects on susceptibility to infection (host defense) induced by immune abnormalities in RA and anti-rheumatoid drugs including methotrexate (MTX) and biological preparations (Bio.), and effects on immune abnormalities and associated inflammation in RA (anti-rheumatoid effects). Concerning the former effects, the effects on Natural killer cell receptor expression were evaluated at the beginning of the 2000s.[11-13] In addition, in a study on the adjuvant effects of Kampo medicines on influenza vaccination (Scientific Research Group supported by a Grant from the Ministry of Health, Labour and Welfare), the courses of immune responses after influenza vaccination in RA patients were observed (Table 1). As a result, the influenza antibody titer did not differ between healthy subjects and RA patients receiving Kampo medicines. In RA patients receiving Kampo medicines, effects comparable to or more marked than those in previous studies in RA patients were obtained, showing no influences of influenza vaccination on the disease activity of RA.[14]

## Anti-rheumatoid effects

For the evaluation of the anti-rheumatoid effects of Kampo medicines, randomized controlled trials (RCTs) are the most important. However, for the evaluation of the effects of Kampo medicines, the accumulation of complete responders is considered to be useful, and we previously reported multiple complete responders.[15] Recently, we encountered a patient with RA developing during postoperative chemotherapy for rectal cancer. In this patient, the disease activity of RA could be controlled by Kampo treatment alone. In such patients, since the influences of strong immune suppression on

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**Table 1** GMTs and fold increase in GMT for influenza A/H3N2, A/H1N1, and B strains in RA patients treated with Kampo formulae before and after administration of influenza vaccines.

| | Total | Without MTX group* | With MTX group** |
|---|---|---|---|
| GMT, mean ± SD | | | |
| A/H1N1 strain | | | |
| Baseline | 12.1 ± 14.0 | 11.0 ± 12.1 | 14.1 ± 15.0 |
| 4 weeks later | 78.8 ± 119.7 | 39.6 ± 39.3 | 115.9 ± 148.8 |
| A/H3N2 strain | | | |
| Baseline | 13.5 ± 13.9 | 16.0 ± 19.7 | 11.7 ± 10.2 |
| 4 weeks later | 35.7 ± 33.6 | 33.1 ± 21.8 | 39.1 ± 40.2 |
| B strain | | | |
| Baseline | 12.8 ± 10.3 | 13.9 ± 9.2 | 11.4 ± 11.5 |
| 4 weeks later | 27.3 ± 27.8 | 22.8 ± 19.2 | 31.4 ± 34.0 |
| Fold increase, mean (range) | | | |
| A/H1N1 strain | 6.5 (1 to 64) | 3.6 (1 to 16) | 8.2 (1 to 64) |
| A/H3N2 strain | 2.6 (1 to 16) | 2.1 (1 to 8) | 3.3 (1 to 16) |
| B strain | 2.1 (1 to 16) | 1.6 (1 to 4) | 2.7 (1 to 16) |

* without MTX group: patients treated with classical DMARDs alone, patients treated with taclolimus hydrate.
** with MTX group: patients treated with MTX, but not biologics.
Abbreviation: GMTs: Geometric mean titers, MTX: methotrexate, DMARD: Disease modifying anti-rheumatic drug.

the underlying disease are unclear, Kampo medicines are extremely useful when they are effective. On the other hand, as we reported in the symposium of this scientific association in 2011, since the appearance of Biologics, the treatment strategies for RA have markedly changed. In this present situation, to clinically make use of the anti-rheumatoid effects of Kampo medicines, the RA patient population who responds to Kampo medicines (responders) should be clarified. In recent years, we have attempted to identify responders to Kampo medicines in terms of both the autoantibody expression pattern in RA patients and the action mechanism (anti-rheumatoid effects) of Kampo medicines. Using these methods, the anti-tumor effects of Kampo medicines can be clinically applied (Figure 1).

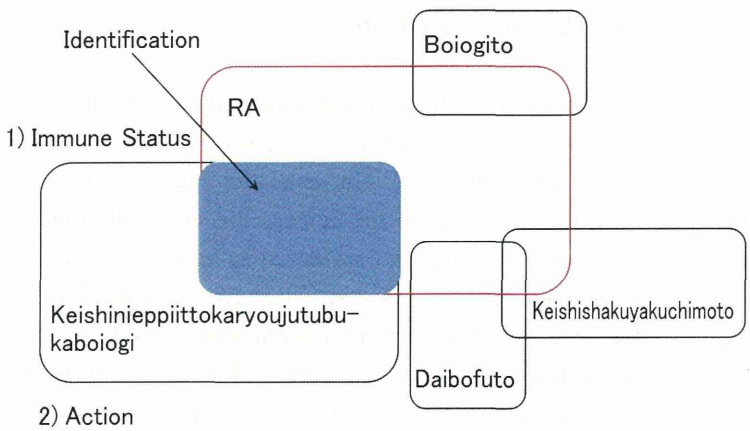


**Figure 1** Identification of Kampo Responders among the patients with RA. One of several Kampo formulae is usually administered to RA patients. Therefore, we first attempt to demonstrate the status of responder to representative formula: Keishinieppiittokaryojutsubu.
The studies to assess traditional concept objectively are divided into 3 groups. Subject of the study is as follows: i) diagnostic methods, ii) traditional pathological concept, and iii) target group of a formula (responders to a formula). The methodology of this scheme applies to the method to detect the target group of a formula (iii). Generally, traditional physical examination has been investigated to determine the target group of a Kampo formula. In contrast, we performed the detection of the responders to a Kampo formula within the patients with RA using 2 methodologies as described below. Because, it is considered that it is impossible to detect the clinical features of responders to a Kampo formula among the patients with varied diseases in Western medicine.
Methodology 1: To clarify the immune status of Kampo responders, Methodology 2: To reveal the action of Kampo formulae on RA.

## Conclusion

We discussed the immunoregulation by Kampo medicines in clinical observations. A lot of immunomoduratory effects of Kampo formulae have been demonstrated *in vivo* and *in vitro*. From now, it is very important to indicate the methodology to clinically make use of the immunomodulatory effects of Kampo medicines.

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*Research Article*

# The Observation of Humoral Responses after Influenza Vaccination in Patients with Rheumatoid Arthritis Treated with Japanese Oriental (Kampo) Medicine: An Observational Study

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*Objective.* The efficacy of influenza vaccination in patients treated with Japanese Oriental (Kampo) Medicine is unknown. The objectives of this study were to observe the efficacy of influenza vaccination in RA patients treated with Kampo. *Methods.* Trivalent influenza subunit vaccine was administered to 45 RA patients who had received Kampo. They were divided into 2 groups: RA patients treated without MTX ("without MTX group") and treated with MTX ("with MTX group"). Antibody titers were measured before and 4 weeks after vaccination using hemagglutination inhibition assay. *Results.* Geometric mean titers (GMTs) of anti-influenza antibodies significantly increased for all influenza strains. Response to the influenza vaccination in RA patients treated with Kampo was not lower than that of healthy subjects and the response in the "with MTX group" had a tendency to be higher than that in RA patients treated with MTX in the previous study. There was no significant difference in the GMT after 4 weeks between the "with MTX group" and the "without MTX group." A decreased efficacy in both seroprotection and seroconversion was not found in the "with MTX group." *Conclusion.* These observations may open the way for further clinical trials to establish the efficacy for the influenza vaccination in RA patients treated with Kampo.

## 1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease that is associated with immunologic changes in T cells and B cells. In patients with RA, an impaired ability to react to antigens and an increased peripheral blood CD4/CD8 ratio has been observed in T cells [1, 2]. The presence of soluble interleukin-2 (IL-2) receptors in serum has showed T cell activation [2, 3]. Furthermore, T cell receptor rearrangement excision circles measured from T cells from RA patients were substantially lower than those in healthy controls, because the T cell receptor repertoire has been oligoclonal, which suggests on antigen selection and restriction of the repertoire [4]. There is also a decline in the thymic output of T cells. This premature aging of T cells in RA may have very severe effects on vaccine responses, which are well known to decrease with aging [5]. Additionally, the function of regulatory T cells (CD4+, CD25+) may be abnormal in active RA patients, with a lack of suppression of CD4+ or CD8+ T cells [6].

The multiple immunologic effects of the disease process may in part explain why patients with RA are considered immunocompromised and at increased risk of infection [7]. Therefore, although the exact prevalence, morbidity, and mortality of influenza in patients with RA are unknown, a yearly influenza vaccination is recommended [8]. The influenza vaccination is safe and results in protective levels of anti-influenza antibodies in most RA patients, even when they are treated with prednisone, disease-modifying antirheumatic drugs (DMARDs), or tumor necrosis factor-blocking agents [9, 10].

In Japan, Japanese traditional herbal (Kampo) Medicine, which is covered by national health insurance, is often

prescribed in the primary care field and is also applied as an alternative treatment for serious diseases such as RA. Since ancient times, many kinds of Kampo formulae have been used traditionally and are found to be clinically effective for RA treatment. These formulae usually contain components from several medicinal plants that are thought to exert anti-inflammation and immune-regulator effects and are effective for treating RA [11–13]. We have demonstrated that kampo formula possessed antirheumatic effects in vitro and in vivo [14, 15]. Furthermore, we have observed that the administration of kampo formula partially suppressed T cell activation in collagen induced arthritis (CIA) mice [16]. However, the effectiveness of the influenza vaccination in RA patients treated with Kampo remedy is still not known. The purpose of this study is to investigate the response to the influenza vaccination in RA patients treated with Kampo remedy.

## 2. Patients and Methods

*2.1. Patient's Profile.* Patients who visited our department in 2010-2011 had to fulfill the American College of Rheumatology 1987 revised criteria for the classification of RA and were selected in a random sampling method. All patients had been treated with Kampo formulae, which were often administered to the patients with RA.

*2.2. Study Design.* An observational study design was utilized in this study. Forty-five patients were entered into this design. Patients received the influenza vaccine intramuscularly from October 2010 until January 2011. Immediately before and 4 weeks after vaccination, blood was drawn for the measurement of C-reactive protein levels (CRP), erythrocyte sedimentation rate (ESR), and anti-influenza antibodies. The Disease Activity Score in 28 joints (DAS28) [17] was recorded before and 4 weeks after vaccination. Information on previous influenza vaccinations was obtained from all participants, and adverse effects occurring in the first 7 days postvaccination were recorded. This study was approved by the Ethics Committee of Gunma Central & General Hospital in Aug 2010.

*2.3. Vaccine.* We used a trivalent influenza subunit vaccine (2010-2011; Daiichi-Sankyo co.ltd Tokyo Japan) containing purified hemagglutinin and neuramidase of the following strains: A/California/7/2009 (H1N1)-like strain (A/H1N1 strain), A/Victoria/210/2009 (H3N2)-like strain (A/H3N2 strain), and B/Brisbane/60/2008-like strain (B strain).

*2.4. Hemagglutination Inhibition Assay (HIA).* The HIA was used for the detection of anti-influenza antibodies. HIAs were performed with guinea pig erythrocytes in accordance with standard procedures [18]. The following parameters for efficacy of the vaccination based on the anti-influenza antibody response were evaluated: geometric mean titer (GMT), fold increase in titer, 4-fold titer rise resulting in a postvaccination level of 40 (seroconversion), and titer rise to 40 $\geq$ (seroprotection). HIA titers 40 are generally considered to be protective in healthy adults [19].

## 3. Results

*3.1. Patient Characteristics.* Forty-five RA patients were administered Kampo treatment. They were divided into 2 groups as follows: 16 RA patients treated without MTX (without MTX group) and 23 RA patients treated with MTX (with MTX group). Patients treated with tacrolimus (TAC) or biologics were excluded from the patients in the without MTX group, and patients treated with biologics were excluded from the patients in both the with MTX and without MTX group. Their characteristics were shown in Table 1.

*3.2. The Response to the Influenza Vaccination.* Each GMT after 4 weeks vaccination was 78.8 $\pm$ 119.7, 35.7 $\pm$ 33.6, and 27.3 $\pm$ 27.3 in A/H1N1, A/H3N2, and B strain, respectively (Table 2). Response to the influenza vaccination in RA patients treated with Kampo formulae was not lower than that of healthy subjects in previous studies [20, 21]. There was no significant difference in the GMT after 4 weeks between the "with MTX group" and the "without MTX group." The GMT in the with MTX group was higher than in the without MTX group (Table 2). The response in the with MTX group had a tendency to be higher than that in RA patients treated with MTX in the previous study [21]. Furthermore, we calculated the fold increase as well as the GMT. The mean fold increase in each group was as follows: 6.5, 2.6, and 2.1, respectively (Table 2). The fold increase in the with MTX group also had a tendency to be higher than in the without MTX group, although this was not significant.

*3.3. Seroprotection and Seroconversion.* After 4 weeks vaccination, the percentage of patients who possessed the 40 $\geq$ titer in A/H1N1 was 53.3, 50.0, and 65.2% in total RA patients, without MTX group and with MTX group, respectively (Figure 1). There was no significant difference between the with MTX and the without MTX groups and a decreased efficacy in seroprotection was not found in the with MTX group. In A/H3N2, the percentage of patients who possessed the 40 $\geq$ titer was 46.7, 50.0, and 52.2%, and in the B strain, 28.9, 25.0, and 39.1% in total RA patients, without MTX group, and with MTX group, respectively. The seroprotection effect observed in the with MTX group had a tendency to be higher than results in the previous study [21]. In seroconversion, the percentage of patients who possessed 40 $\geq$ titer induced by 4-fold increase was 40.0, 35.6, and 15.6%, respectively (A/H1N1, A/H3N2, and B Strain). There was no significant difference between the with MTX and the without MTX groups also in seroconversion (data not shown).

*3.4. The Influence of Influenza Vaccination upon RA Disease Activity.* The DAS28 did not change after vaccination. There was no adverse reaction by influenza vaccination.

## 4. Discussion

Kampo medicine, which is covered by national health insurance in Japan, is often prescribed in the primary care field,

Table 1: Characteristics at baseline of RA patients in this study.

| | Total | Without MTX group* | With MTX group** |
|---|---|---|---|
| Age, mean ± SD years | 56.2 ± 13.5 | 58.6 ± 10.5 | 54.1 ± 12.6 |
| No. (%) female/No. (%) male | 42 (93)/3 (7) | 15 (94)/1 (6) | 22 (92)/2 (8) |
| Duration of RA mean ± SD years | 12.2 ± 14.1 | 13.5 ± 15.6 | 10.9 ± 11.6 |
| MTX dosage, mean ± mg/week | 5.1 ± 3.8 | 0 | 7.6 ± 2.5 |
| PSL dosage, mean ± SD mg/day | 2.1 ± 2.0 | 1.6 ± 1.5 | 2.4 ± 1.9 |
| Taking DMARDs, No. | | | |
| Bucillamine | 1 | 1 | 0 |
| Sulfasalazine | 11 | 8 | 2 |
| Tacllolimus | 4 | 0 | 4 |
| DAS28 CRP | 3.2 ± 1.1 | 2.9 ± 1.0 | 3.3 ± 1.4 |

*Without MTX group: patients treated with classical DMARDs alone. Patients treated with tacllolimus were excluded. **with MTX group: patients treated with MTX, but not biologics.

Table 2: GMTs and fold increase in GMT for influenza A/H3N2, A/H1N1, and B strains in RA patients treated with Kampo formulae before and after administration of influenza vaccines.

| | Total | Without MTX group* | With MTX group** |
|---|---|---|---|
| GMT, mean ± SD | | | |
| A/H1N1 strain | | | |
| Baseline | 12.1 ± 14.0 | 11.0 ± 12.1 | 14.1 ± 15.0 |
| 4 weeks later | 78.8 ± 119.7 | 39.6 ± 39.3 | 115.9 ± 148.8 |
| A/H3N2 strain | | | |
| Baseline | 13.5 ± 13.9 | 16.0 ± 19.7 | 11.7 ± 10.2 |
| 4 weeks later | 35.7 ± 33.6 | 33.1 ± 21.8 | 39.1 ± 40.2 |
| B strain | | | |
| Baseline | 12.8 ± 10.3 | 13.9 ± 9.2 | 11.4 ± 11.5 |
| 4 weeks later | 27.3 ± 27.8 | 22.8 ± 19.2 | 31.4 ± 34.0 |
| Fold increase, mean (range) | | | |
| A/H1N1 strain | 6.5 (1 to 64) | 3.6 (1 to 16) | 8.2 (1 to 64) |
| A/H3N2 strain | 2.6 (1 to 16) | 2.1 (1 to 8) | 3.3 (1 to 16) |
| B strain | 2.1 (1 to 16) | 1.6 (1 to 4) | 2.7 (1 to 16) |

*Without MTX group: patients treated with classical DMARDs alone. Patients treated with tacllolimus were excluded. **with MTX group: patients treated with MTX, but not biologics.

and is also applied as an alternative remedy for RA. The efficacy for RA of Kampo medicines has been demonstrated by case or case series reports and several clinical trials. From these reports, the clinical effectiveness of Kampo therapy is almost similar to that of classical DMARDs, such as bucillamine (Bc) and salazosulfapyridine (SASP). Additionally, several investigators have demonstrated the immunomodulatory effects of Kampo medicine in RA patients as well as an arthritis mouse model, such as CIA [11, 12, 14]. We have also reported that Kampo therapy resulted in a decrease in serum IL-6 levels, but not TNF-$\alpha$ levels, as well as the suppression of arthritis development, based on the observations of the CIA mouse model [15]. Furthermore, it has been reported that Kampo medicine is probably effective against infection. The efficacy of Kampo therapy on atypical mycobacterium pneumonia and aspiration bacterial pneumonia has been demonstrated [22, 23], and these effects may be caused by immune-regulator effects, but not direct antibacterial effects. On the other hand, RA patients are susceptible to both viral and bacterial infections. In Japanese RA patients, major causes of death included malignancies (24.2%), respiratory involvement (24.2%) including pneumonia (12.1%) and interstitial lung disease (ILD) (11.1%), cerebrovascular disease (8.0%), and myocardial infarction (7.6%) [24]. Infectious disease is one of the critical factors in the mortality of RA patients. Therefore, a yearly influenza vaccination is recommended by the Center for Disease Control and Prevention (CDC) [25, 26]. However, the immune response to the influenza vaccination has not been reported in RA patients treated with Kampo medicine. This is the first report demonstrating the titer of anti-influenza antibodies before and after influenza vaccination in RA patients administered Kampo formulae.

The response to the influenza vaccination in our population was almost similar to previous results in healthy subjects. Kampo therapy may be beneficial for RA patients from the clinical viewpoint of protection against influenza

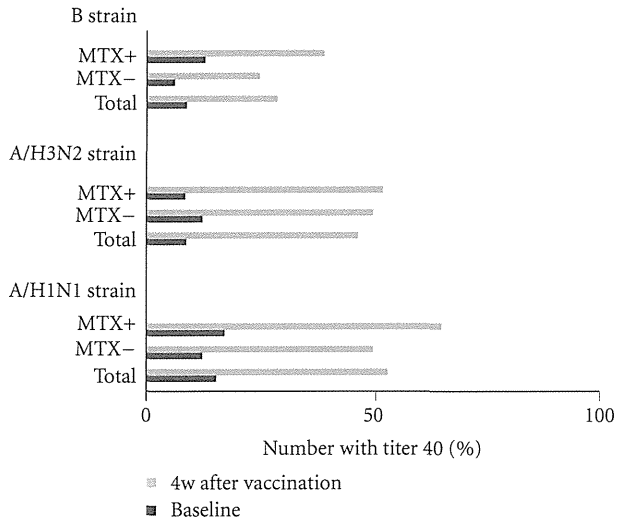


FIGURE 1: Percentage of patients with anti-influenza titers ≥40, as determined by a hemagglutination inhibition assay for each strain after vaccination with a trivalent influenza subunit vaccine, in total RA patients, RA patients treated with MTX, and RA patients treated without MTX. Solid bars represent prevaccination titer ≥40; open bars represent post vaccination titer ≥40.

virus infection as well as suppression of RA disease activity. However, there are various opinions about the efficacy of the influenza vaccination in RA patients. Some reports demonstrate both no differences and significant differences in the response rate between treatment with and without MTX in RA patients [20, 27–29]. This discrepancy may be caused by the different endpoints when measuring the response to the influenza vaccination and different influenza virus roots. Therefore, our data should be limited in reference to the adjuvant effects of Kampo therapy. However, as the baseline titers in this study were less than previous studies, we consider Kampo therapy to be partially beneficial for RA patients in seroprotection and seroconversion. In addition, it has been reported that the response to vaccination was significantly less in patients treated with anti-TNF-a and anti-CD20 antibody (rituximab) drugs than RA patients without biologics [21, 29]. We have checked the titers of the 5 patients treated with biologics, and they were less than those of other RA patient groups (data not shown). Kampo therapy may not influence the response to the influenza vaccination in RA patients treated with biologics. To analyze this problem, further clinical observational studies will be required using a large number of patients.

The RA disease activity by DAS28 did not change after vaccination in our patients. It is generally thought that the vaccination does not influence the disease activity and the titer of the serological markers. A recent report demonstrates that influenza vaccination did not alter the percentage of healthy adults with positive autoantibodies [30].

We have reported several patients with MTX-resistant RA as being successfully treated with Kampo medicine; however, it is still not clear as to how Kampo medicine acts on arthritis in humans [31]. We previously demonstrated that Kampo medicine suppressed polyclonal B cell activation, but not T cell activation, significantly in the CIA mouse model [14, 15]. Recently, it has been clarified that the development of arthritis in the CIA mouse contributed to the differentiation of IL-17 producing cells (Th17), dependent on IL-6 and TGF-$\beta$ [32, 33]. In our previous study using CIA, Kampo medicine decreased the serum IL-6 levels, but not TNF-$\alpha$, suggesting that the suppression of Th17 cell activation by Kampo therapy probably improved the development of arthritis. Thus, we suggest that Kampo medicines do not influence the function of antigen presentation in dendrite cells or macrophages. Based on these findings, we suggest that Kampo therapies do not suppress the response to the influenza vaccination in RA patients. Besides, in innate immunity, we have demonstrated that Juzentaihoto enhanced the production of iNOS in macrophages [34] and the upregulation of NK receptor's expression (Killer-cell immunoglobulin-like receptors) in NK cells [35]. Additionally, the direct anti-influenza virus actions of cinnamon cortex and ephedrae herba (the main herbs composing kampo formulae) have been demonstrated, while these actions are not associated with the response to vaccination in RA patients treated with Kampo [36, 37].

In conclusion, we have demonstrated the changes in the titer of each anti-influenza antibody before and after vaccination in RA patients treated with Kampo formula. A low response to the vaccination was not observed compared with previous studies, and in the MTX-treated patients group, the response to vaccination was higher in our study than in previous reports. The present observations may open the way for further clinical trials to establish the efficacy for the influenza vaccination in RA patients treated with Kampo medicines.

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Symposium in the 28th Annual Meeting of Medical and Pharmaceutical Society for WAKAN-YAKU
"The forefront of clinical research on Wakan-yaku (traditional Japanese medicines)"

# Therapeutic strategies for rheumatoid arthritis -Recent topics on Japanese Oriental (Kampo) medicine-

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## Introduction

Rheumatoid arthritis (RA) is one of the diseases for which Kampo medicine has been clinically used for a long period.[1-3] Various Kampo prescriptions such as boiogito, keishikajutsubuto, and yokuininto have been administered to patients with RA, playing a certain role in therapeutic strategies for RA in Japan.[4-6]

Therapeutic strategies for RA have markedly changed. Methotrexate (MTX), which began to be clinically applied for RA in the 1960s, was confirmed to be effective against RA by large-scale controlled trials in the 1980s.[7] Since the end of 1990s, biological agents (infliximab in Japan since 2003) have been clinically used. At present, strict control of biological agents is recommended. To achieve this, the ACR/EULAR classification criteria were established in 2009.[8] The induction rate of clinical remission using biological agents is 40-50%, and the induction of clinical remission still remains a difficult problem. However, compared with results using conventional DMARDs, those using biological agents are excellent.

With this background, we discuss the role and position of Kampo medicine in RA treatment.

## Responders to Kampo medicines

Until the 1990s, there have been case reports showing the effects of various Kampo medicines on RA. The major medicines used included keishikaryojutsubuto, boiogito, and eppikajutsuto (or their combinations), and yokuininto, juzentaihoto, and daibofuto. In addition, the effects of makyoyokukanto and hochuekkito have also been reported.[9-11] However, in many case reports showing the effects of these Kampo medicines on RA, changes in symptoms, erhythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or rheumatoid factor (IgM-RF) were evaluated, and the Lansbury activity index was used for comprehensive evaluation. This was not a problem since these parameters were also used by the Japan College of Rheumatology (JCR) until 1990s. After 2000, with the advent of potent drugs, the diagnosis and evaluation of RA have become more objective. We can only speculate about whether previous reports on Kampo medicines fulfilled such diagnostic and evaluation criteria. However, we consider that there were marked responders to Kampo medicines even employing the present evaluation methods used in 2011.

We administer crude drugs (decoctions) to 80-90% of patients with RA, and these patients often exhibit pathological conditions in Kampo medicine (Syndrome: so-called "SHO" in Japanese Oriental Medicine)[12] indicated for keishinieppiittokaryojutsubu (KER). Since the latter half of the 1980s, we have reported the effectiveness of this prescription, and encountered some patients who showed favorable responses and clinical remission even using a recent evaluation method.[13] (Fig. 1)

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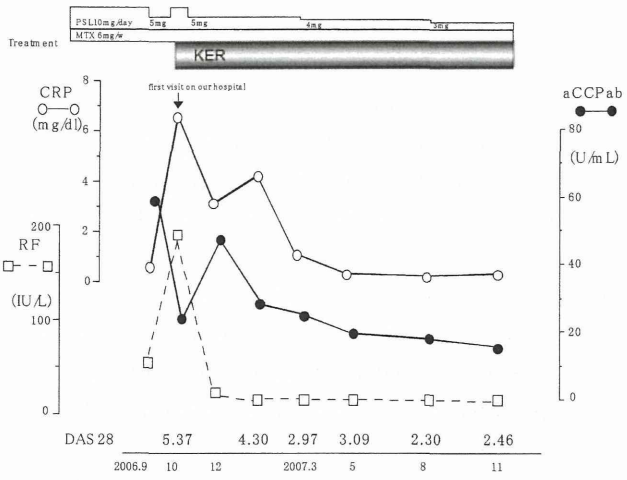


**Fig. 1** Clinical course A 57-year-old female
She was an RA patient within 1 year after onset showing high activity (DAS28CRP, 5.37). Due to resistance to MTX (6 mg), KER was administered. A favorable response in terms of DAS28CRP was observed, and aCCPab also gradually decreased. She was a marked responder to the Kampo medicine.

medicines among RA patients showing extremely high activity. Therefore, the clarification of the subtypes of RA that respond to Kampo medicine, i.e., use of the methodology called "objectification of SHO" in RA may be a promising method (Fig.2).

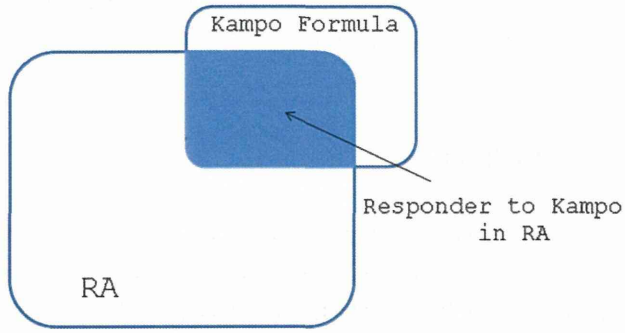


**Fig. 2** Objectification of "SHO: Kampo diagnosis" (Syndrome) in RA
Clarification of the subtypes (closed space) of RA that respond to Kampo medicines using the parameters in the Western medicine, but not traditional methodology.

## Clinical characteristics of responders

As described in the above section, there are responders to Kampo medicines among RA patients. However, in terms of recent therapeutic strategies for RA, it may be difficult to administer Kampo prescriptions for some months-some years while observing their effects as was performed in the 1990s. In 2008, the American College of Rheumatology (ACR) regarded the "window of opportunity" as 6 months, and recommended the use of a TNF inhibitor in combination with MTX in RA patients within 3 months after onset who show high disease activity and have no problems regarding the payment of medical costs.[14] Based on this recommendation, the JCR also recommended considering biological agents even 3 months after onset in the presence of the progression of bone erosion or disease activity score (DAS) 28-ESR > 3.2. In this trend, to utilize the effects of Kampo medicines in clinical practice, the following method can be considered first; patients with high activity are excluded based on DAS28, and Kampo medicines are clinically administered only to patients with mild-moderate activity, which is similar to the method of using disease-modifying antirheumatic drugs such as Salazosulfapyridine (SASP) and Bucillamine (Buc). However, there are responders to Kampo

We previously reported a characteristic of responders to Kampo medicines based on the basal value of anti-CCP antibody (aCCP) titer as a prognostic factor of RA and its changes after treatment. In brief, there were two findings indicating responders to Kampo medicines: i) The aCCP titer is not high even if positive, and ii) even if the aCCP titer is high, it decreases 3 months after treatment.[15] At present, to clarify more detailed patterns, comprehensive analysis of autoantibody expression patterns is in progress.

If we are able to demonstrate the subtype of RA that respond to Kampo, the use of herbal medicine including Kampo by RA patients will be becoming increasingly popular in several developed states such as USA.[16]

## Conclusion

We discussed the possibility of Kampo treatment in the present RA classification criteria and therapeutic treatment. Kampo medicine is "personalized medicine". Although there are marked responders, patients to whom Kampo medicines should be administered cannot be clarified until effects are confirmed after administration following diagnosis based on conventional medi-

cine. However, in rheumatology, there are also no useful clinical markers to predict the effects of biological agents and low molecular weight anti-rheumatic drugs before administration. RA is a heterogeneous disease. We consider that Kampo medicines will continue to play an important clinical role in RA treatment from various aspects in the future.

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Integrative Medicine Insights



CASE REPORT

# Edematous Erythema at the Hands and Feet Probably Caused By the Traditional Herb "Radix Astragali"

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**Abstract**

**Objective:** To describe a patient with erhythema and edema after Radix Astragali was added to a kampo formula.

**Case summary:** A 21-year-old male, who was diagnosed as having atopic dermatitis in 1989, demonstrated systemic dry eruptions and consulted our department for treatment with traditional herbal medicine (THM) in 2004. The oral administration of herbal medicine resulted in decreased symptoms as well as a reduction in the serum IgE level. In August 2007, he complained of sweating on the neck and we added Radix Astragali to the previous formula. About 18 hours after he ingested the new formula including Radix Astragali, erhythema appeared with swelling of the bilateral hands and feet. Administration of the formula was discontinued and about 48 hours later, his symptoms had almost disappeared. Astragaloside, which is the main ingredient of Radix Astragali, was negative on lymphocyte transforming test (LTT) and we could not determine the ingredient that induced erhythema.

**Conclusion:** We consider that the Radix Astragali induced acute erhythema with swelling based on the clinical course. Acute edematous erythema due to THM is very rare and we discuss allergic reactions to traditional herbs and review the litrature.

**Keywords:** Radix astragali, erhythema, allergic reaction, lymphocyte transforming test, traditional herbal medicine (Kampo)

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## Introduction

Radix astragali, *Ogi*[R] is prepared from the root of Astragalus membranaceus Bunge or A. mongholicus Bunge, and is one of the representative herbs used in the field of traditional herbal medicine (THM: called Kampo in Japan). The main components consist of flavonoids such as formononetin, 3'-hydroxyformononetin, l-canavanin and saponins such as astragaloside, sayasaponin. This herb is usually used in the form of decoctions having a tonic-effect. It has been reported that this drug has pharmacological actions such as immunomodulatory effects, anti-inflammatory effects and anti-allergic effects.[1,2]

This paper describes a rare case of a patient with atopic dermatitis (AD) demonstrating edematous erythema thought to be caused by adding Radix astragali to a kampo formula.

## Case Report

The patient consulted our hospital in April 2004 at 21 years of age, with systemic dry eruptions associated with AD.

In 1989, he developed systemic eruption with itching and was diagnosed as having AD at a local hospital. He was treated with ointment containing steroids and his condition periodically became somewhat better or worse. However, his symptoms gradually worsened recently and the use of ointment containing steroids was discontinued. Thereafter, he consulted our hospital with a request for herbal medicine in 2004. At the first medical examination in April 2004, he had severe dry eruptions on the neck, chest, bilateral upper and lower extremities, especially, eczema with lichen on the neck. His laboratory data were as follow: White blood cell: 7400/mm$^3$, eosinophil: 14.9%, immunoglobulin (Ig)-E: 15012.6 mg/dl, C-reactive protein (CRP): 0.1 mg/dl, lactate dehydrogenase (LDH): 226IU/l. Hepatic, renal and thyroid function was normal. Kagen-ichiin-sen (KIS; decoction: Uchida Co. Ltd Tokyo Japan; Table 1 ) was prescribed per mouth daily, based on the traditional diagnostic system.[3] Briefly, the indications for KIS are eczema and pruritis with dry skin and dotty or diffuse pigmentation. The oral intake of KIS resulted in a decrease in symptoms as well as a reduction of the serum IgE level (3863.7 mg/dl) on Feb. 2007.

**Table 1.** Herbs composed of Kagenichiin-sen.

| Component | Volume (gram) |
|---|---|
| Radix rehmanniae | 20 |
| Radix paeoniae | 6 |
| Ophinopgonis tuber | 6 |
| Lycii radicis cortex | 3 |
| Anemarrhenae rhizoma | 3 |
| Radix glycyrrhizae | 3 |
| Asini corli collas | 1 |
| Chinemys reevesii | 0.5 |
| *Radix astragali** | 5 |

**Note:** The herbs were mixed with 600 mL of water and boiled down to 300 mL, and the aqueous extract was filtered through a sieve. The extract, called a decoction, was administered 3 times a day before meals. *Astragali Radix was added on Aug 2007.

In August 2007, he complained of sweating on the neck and we added Radix Astragali to KIS, since the indication for Radix Astragali is eruptive eczema with sweat.[3] However, about 18 hours after he ingested the full day's dose (twice a day) including Radix Astragali, erhythema with swelling of the bilateral hands and feet appeared (Fig. 1A). There was no swelling of the superficial lymph nodes. Although the eosinophil count and serum LDH level did not change, the serum

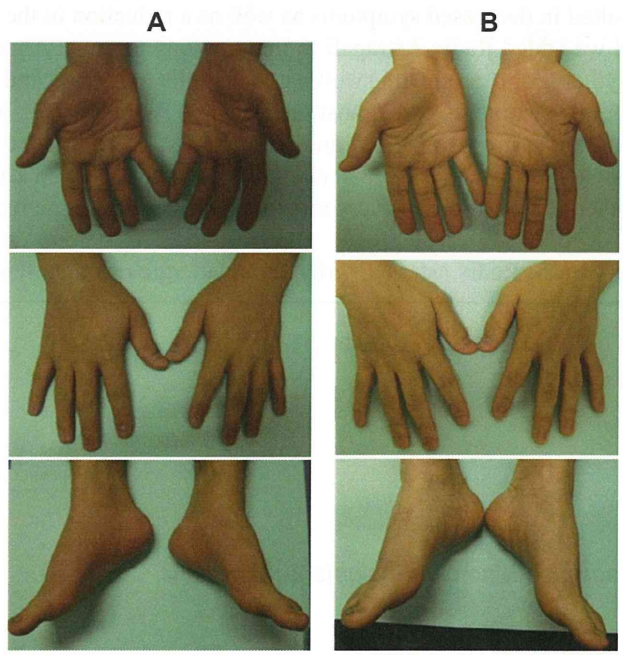


**Figure 1. A**) Eighteen hours after administration of Radix Astragali. Edematous erythema with a sensation of heat at the hands and feet. Upper panel: the palm, Middle panel: the back of hands, Lower panel: feet. **B**) Forty-eight hours after discontinuation of Radix Astragali intake. Edematous erythema had almost disappeared.

CRP level increased slightly (0.3 mg/dl). Anti-nuclear antibody was negative, and there were no apparent monoclonal gammopathies. Administration of the altered formula was discontinued and 2 days later, his symptoms had almost disappeared (Fig. 1B) and the serum CRP level was <0.1 mg/dl. Thereafter, he continued intake of the original KIS formula and his condition stablized.

## Analysis by LTT using herbal ingredient

The patient refused oral provocation with a low concentration of Radix Astragali. Therefore, lymphocyte transformation test (LTT) was performed with his consent. LTT for THM is unreliable because of the likelihood of a false positive results.[4] Thus, LTT for the main ingredient of Radix astragali was utilized, and as a result astragaloside was negative on LTT (Table 2). This assessment was approved under the comprehensive agreement provided by Gunma University Hospital.

## Discussion

THM, which is covered by national health insurance in Japan, is generally used in the field of primary health care, and is also administered as an alternative remedy for chronic diseases such as AD. Although it is considered that THM is generally a safe drug, some adverse effects are known. Drug eruption is an occasional adverse effect in THM and several cases have been reported.[5–11] Recently reported cases of drug eruptions due to THM are summarized in Table 3. Discontinuation of each drug resulted in the improvement of drug eruptions in all cases. Two cases of drug eruption induced by Radix Astragali have been reported, one patient (No. 7) showed lichenoid planus 3 weeks after the start of Radix Astragali intake. In contrast, another patient (No. 2) showed edematous erythema with fever and oliguria that appeared 24 hours after taking medicines containing Radix Astragali. Although physicians consider that drug eruption due to THM is generally mild, it should be understood that a few patient may show acute edematous erythema such as erythroderma. Generally, erythema with a heat sensation in erythroderma spreads over the whole body within 12–48 hours. The present case also showed edematous erythema 18 hours after the drug-intake, but erythema involved the hands and feet. It is unclear whether the present patient would have developed an acute erythroderma if the administration of Radix astragali had continued.

Incidentally, in this case it was nesessary to rule out hereditary/acquired angioedema in the differential diagnoses. Unfortunately, we failed to measure the complements (eg, Serum C1q/C3/C4) and C1 esterase inhibitor. Therefore, we are not able to diagnose the allergic edematous erythema more precisely. However, we regarded the clinical manifestation of the present patient as allergic edematous erythema because of the improvement following discontinuation of drug, absence of monoclonal gammanopathy and absence of any classification for autoimmune diseases.

Although Radix astragali have several bioactivities such as immunomodulatory and the vasodilative effects,[1,2] there was a limited quantity of the components of Radix astragali in the decoction. Therefore, edematous erythema is probably induced by an allergic response to Radix astragali. Generally, it is difficult to confirm that a traditional herb must be the causative drug in an allergic reaction. LTT for THM is unreliable because of the likelihood of false positive results.[4] Therefore, we performed LTT using only the main component of Radix astragali. However, the causative ingredient could not be confirmed. There are two possibilities for these results: one is the likelihood of a causative components other than astragaloside and another is that plural components (crude drug) may be associated with the allergic reaction.

**Table 2.** The results of lymphocyte transformation test for herbal ingredients.

| | No treatment | PHA# | Astragaloside | Saikosaponin** |
|---|---|---|---|---|
| Max response (cpm) | 144 | 1999303 | 172 | 199 |
| Max S.I.* | 1 | 1384.0 | 1.2 | 1.4 |

**Notes:** *Stimulation Index: astragaloside or saikosaponin/no treatment; **Saikosaponin was utilized as negative control among herbal ingredient, #PHA, phytohemagglutinin.

**Table 3.** List of recently reported cases of drug eruptions due to THM.*

| Patient no. author | Year (Ref. no.) | Causative drug | Basic disease | Interval until onset | Type of drug eruption | Results of allergic test | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | LTT** | Patch test | OIT*** |
| 1. Okuda T, et al | 1995 (5) | Sinomeni Caulis et Rhizoma; Boi | Rheumatoid arthritis | 2 weeks | Erythema papule | ND# | ND | Positive |
| 2. Noda T, et al | 1997 (6) | Astragali Radix; Ogi | Atopic dermatitis | 24 hours | Edematous erythema | Negative | Positive | ND |
| 3. Ueda D, et al | 2001 (7) | Rehmanniae radix; Jio | Cancer of pharynx | 48 hours | Bullous erythema | Positive | Positive | ND |
| 4. Gushi A, et al | 2001 (8) | Chinese herbs** | Chronic urticaria | 1.5 years | Erythema papule | Positive | ND | Positive |
| 5. Matsumoto K, et al | 2003 (9) | Ephedra herba; Mao | Common cold | 48 hours | Solitary fixed erythema papule | ND | Positive | ND |
| 6. Kubota S, et al | 2004 (10) | Ephedra herba; Mao | Upper respiratory inflammation | 48 hours | Erythema papule | ND | Negative | Positive |
| 7. Momose Y, et al | 2004 (11) | Astragali Radix; Ogi | Colon cancer | 3 weeks | Lichenoid planus | ND | Negative | Positive |
| 8. Kogure T, et al | 2010 (This case) | Astragali Radix; Ogi | Atopic dermatitis | 12 hours | Edematous erythema | Negative$ | ND | ND |

**Notes:** *THM, Traditional herbal medicines; **LTT, Lymphocyte transforming test; ***OIT, Oral ingestive test. #ND, not done; $, LTT for ingredient (astragaloside) but not crude drug was performed.

In fact, it is considered that interstitial pneumonia induced by Shosaikoto is probably an allergic reaction for the crude drug: shosaikoto.[12] To certify the causative drug in the field of dermatology, patch test using crude drug has became prevalant. Evaluating previous reports, the patch test was carried out in 5 cases (No. 2, 3, 5, 6, 7 in Table 2). Three cases (No. 2, 3, 5) showed positive results and the causative drug was determined. In contrast, 2 patients (No. 6, 7) had negative results, but interestingly, these patients agreed to an oral ingestion challenge test and showed positive results. Therefore, we consider that assessment of the clinical course must be important when prescribing crude drugs such as traditional herbs.

Another important question is whether a high serum level of IgE may have been associated with the occurrence of allergic edematous erythema in this patient. There is no report demonstrating that drug allergy occurs more often in patients with AD in comparison with healthy subjects. Based on several investigations,[13,14] it is generally considered that a high serum level of IgE in AD patients is a result, not a cause. However, it is known that a high serum IgE condition increases IgE-mediated type I hypersensitivity reaction through Fc ε receptorI (Fc ε RI) on mast cells.[15] Possibly, edematous erythema having occurred in this patient was caused by an IgE-mediated allergic mechanism. Therefore, it is possible that edematous erythema might have been induced by Radix astragali due to the high serum levels of IgE in this patient. However, we could not identify a causative component using LTT. Since LTT examines lymphocyte (non-IgE)-mediated allergic reactions, LTT might fail to show the positive result.

Herein, we presented a case of an atopic dermatitis with acute edematous erythema caused by Radix astragali. While the causative component could not be determined by LTT, it is estimated that the edematous erythema must have been caused by Radix astragali based on the clinical course of this patient. In eruptions caused by crude drugs, the causative agent should be determined from a comprehensive perspective.[5]

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## Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material. Written consent was obtained from the patient or relative for publication of this study.

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Integrative Medicine Insights



CASE REPORT

# Effect of Kampo Medicine on Pain and Range of Motion of Osteoarthritis of the Hip Accompanied by Acetabular Dysplasia: Case Report and Literature Review

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**Abstract:** We report a 52-year-old female with end-stage osteoarthritis of the hip accompanied by acetabular dysplasia in whom quality of life (QOL) was improved by Kampo treatment.

When she was 42 years old, she developed pain in the left hip joint, and early-stage OA of the hip was diagnosed by hip joint x-ray. Therefore, she took NSAIDs, and received conservative therapies such as diet and muscle training. However, pain in the hip joint increased and her activity of daily life (ADL) decreased at the age of 50, although she continued to receive the conservative therapies. At the age of 52, she consulted our department requesting Japanese Oriental (Kampo) Medicine. Kampo formulae; Keishikaryojutsubuto (12Tab/day: Kuracie Co. Ltd. Japan), and Boiougito (7.5 g/day: Kuracie Co. Ltd. Japan), were administered. Treatment for 3 months resulted in a decrease in the left hip joint pain using visual analogue scale (VAS) and improvement of her ADL. One year later, her joint symptoms have not increased, and both the Harris hip score and the clinical evaluation criteria of osteoarthritis of the hip have improved.

The course of this disease varies depending on the lifestyle of the patient, and Kampo formulations may offer safe, potent supplemental treatment.

**Keywords:** Kampo, acetabular dysplasia, OA of the hip, conservative therapy

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## Introduction

Osteoarthritis (OA) of the hip induces regressive changes in the hip joint cartilage and subsequent abnormality in the synovial membrane and articular capsule, leading to the impairment of joint function, and osseous changes also occur. The prevalence of this disease is not high,[1] but coxalgia and surrounding pain and limitation of the range of motion occur, and subsequently limit ADL with the progression of lesions.

OA of the hip is classified into primary and secondary cases based on the presence or absence of causes. Primary OA of the hip is defined as coxarthrosis with normal hip joint alignment and acetabular formation.[2] In Japan, primary cases account for only 0.65%, and many cases are secondary.[2] The cause of secondary OA of the hip in which lesions are localized in the hip joint includes congenital hip joint dislocation, acetabular dysplasia, necrosis of the femoral head, and Perthes's disease. When acetabular dysplasia remains in the growth period, it may become OA of the hip.[3] When the femoral head is impaired with the treatment of congenital hip joint dislocation, deformation of the femoral head and neck occurs. These are the most frequent causes of secondary OA of the hip.

The natural course of this disease is diverse and classified based on the severity of joint deformation into pre-, early, progressive, and end-stage coxarthrosis, but it does not necessarily progress with aging. The natural course is influenced by the lifestyle, and it has been reported that X-ray radiographic findings improved in some cases.[4] Conservative or surgical treatment is selected in the natural course, and the timing is dependent on individual cases. In Japan, Kampo has been clinically applied for rheumatic diseases for centuries. In this study, we applied Kampo for progressive to end-stage coxarthrosis in a female in her 50 s, and achieved improvement of the hip joint function and QOL. Herein, we report the case along with a literature review.

## Case Report

We encountered a 52-year-old woman with end-stage OA of the hip accompanied by acetabular dysplasia in whom the quality of life (QOL) was improved by Kampo treatment.

She had demonstrated acetabular dysplasia at birth, and dislocation of the hip was treated with a plaster cast. Although anterior coxarthropathy was noted by a general practitioner at the age of 31, she was observed without treatment, due to the absence of joint symptoms. At the age of 42, she developed pain in the left hip joint, and early-stage OA of the hip was diagnosed. Therefore, she took non-steroidal anti-inflammatory drugs (NSAIDs), and received conservative therapies such as diet and muscle training. However, pain in the hip joint increased and her ADL decreased at the age of 50. Nevertheless, she continued to receive conservative therapies, although her symptoms did not change. At the age of 52, she consulted our department requesting Japanese Oriental (Kampo) Medicine. There were no abnormalities on blood and biochemical analysis. Hip joint X-ray showed end-stage OA in the left hip joint (Fig. 1). We administered the Kampo formulae; Keishikaryo-jutsubuto (12Tab/day: Kracie Co. Ltd. Japan), and Boiougito (7.5 g/day: Kracie Co. Ltd. Japan), according to the traditional diagnostic system[5]. The arthralgia was evaluated by visual analogue scale (VAS). Treatment for 3 months resulted in a decrease in hip joint pain as well as improvement of her ADL. One year later, her joint symptoms have not increased, and both the Harris hip score[6] and the Japanese Orthopaedic Association (JOA) hip score[7] have improved (Table 1). Although Kampo treatment continued over one year without discontinuation, there were no adverse effects.

## Discussion

Osteoarthritis of the hip begins with degeneration or wear of the joint cartilage, and various articular

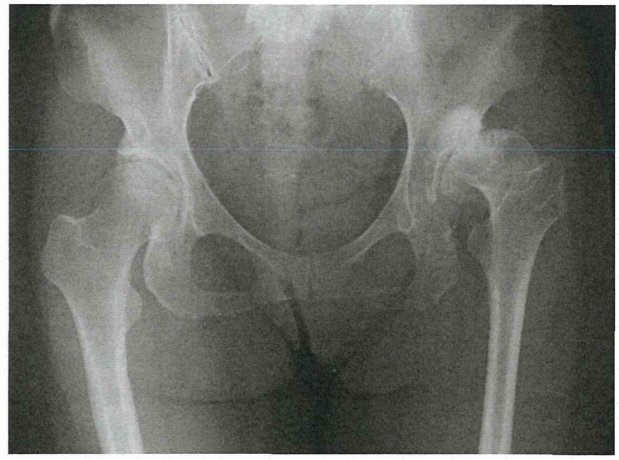

**Figure 1.** Hip joint X-ray. The image shows joint space narrowing, osteosclerosis and osteophyte formation in left hip joint, accompanied by the dysplastic hip.