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A case of rheumatoid arthritis with a decrease in the serum concentration of soluble CD23 by traditional herbal medicine

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Abstract

Traditional herbal (Kampo) medicine for the treatment of rheumatoid arthritis (RA) has not been evaluated for changes in immune status during its use, although several anti-inflammatory effects have been studied *in vitro*. In this case report, we describe a 32-year-old Japanese female with RA who was effectively treated with the Kampo medicine, *Hochu-ekki-to* (Bu-Zhong-Yi-Qi-Tang, 補中益気湯). This treatment decreased the serum concentration of soluble CD23 (sCD23) and RA activity, in addition to tumor necrosis factor-α.

These findings suggest that the therapeutic action of herbal medicine might be attributable to suppression of B cell activation.

Key words Kampo treatment, Immunomodulation, clinical course, case report.

Introduction

Traditionally, many kinds of Kampo formula have been used to treat patients with rheumatoid arthritis (RA) in China and also in Japan. In the last decade, the therapeutic effects have begun to be recognized by certain methods of evaluation in Western medicine.[1] Additionally, the actions of Kampo formulae have been analyzed extensively.[2-4] Several ingredients contained in traditional herbs have been found to exert anti-inflammatory effects.[5-7] Recent study has shown that Kampo treatment suppresses the development of arthritis in a mouse model.[8] However, possible changes in immune status during RA treatment with herbal medicine have not been investigated.

Soluble CD23 molecule (sCD23) is often used as B cell activation marker to evaluate the status of autoimmune diseases.[9-11] We demonstrated that serum levels of sCD23 are elevated correlated with the levels of IgM-rheumatoid factor (IgM-RF) in patients with RA.[11] This molecule enhances the interferon-γ-induced release of tumor necrosis factor-alpha (TNF-α) from monocytes.[12]

Here, we present a case of RA showing a decrease in serum concentration of soluble CD23, as well as improvement in the joint symptoms, by the Kampo formula *Hochu-ekki-to* (Bu-Zhong-Yi-Qi-Tang, 補中益気湯).[13]

Case report

A Japanese woman developed polyarthralgia, particularly in the bilateral knee joints, in April 1985 at the age of 24. Subsequently, she complained of bilateral wrist and elbow joint pain. She was examined at a nearby hospital, found to have IgM-RF, and was diagnosed with RA. She was treated with 15 mg/day of prednisolone (PSL) and 240 mg/day of

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Table I Kampo formulae used in the treatment for the present patient

Kampo formulae	Components	Indications*
Hochu-ekki-to (Bu-Zhong-Yi-Qi-Tang)	Astragali Radix 4.0 Ginseng Radix 4.0 Bupleuri Radix 2.0 Aurantii Nobilis Pericarpium 2.0 Cimicifugae Rhizoma 1.0 Atractylodis Lanceae Rhizoma 4.0 Angelicae Radix 3.0 Zizyphi Fructus 2.0 Glycyrrhizae Radix 1.5 Zimgiberis Rhizoma 0.5	Weak physical condition during recovery, tuberculosis, anemia, loss of appetite, mild fever, dysfunction of the digestive system
Toki-shakuyaku-san (Dang-Gui-Shao-Yao-San)	Paeoniae Radix 4.0 Atractylodis Lanceae Rhizoma 4.0 Alismatis Rhizoma 4.0 Angelicae Radix 3.0 Hoelen 4.0 Cnidii Rhizoma 3.0	Especially correspondent for girls and women with weak physical constitution, anemia, mild edema, weakness of muscles, fatigue, dysmenorrhea, conditions pathologic during pregnancy and after delivery
Keishi-ni-eppi-itto-ka-ryojutsubu (Gui-Zhi-Er-Yue-Bi-Yi-Tang-Jia-Ling-Zhu-Fu)	Cinnamomi Cortex 2.5 Paeoniae Radix 2.5 Glycyrrhizae Radix 2.5 Ephedrae Herba 2.5 Zimgiberis Rhizoma 3.5 Zizyphi Fructus 3.0 Gypsum Fibrosum 3.0 Hoelen 3.0 Atractylodis Lanceae Rhizoma 3.0 Aconitii Tuber 1.0	Physically weak patients, red face, cold feet, pain of joints and muscles accompanied by sweating morning stiffness of finger joints, edema, oliguria
Kyuki-choketsu-in (Xong-Gui-Tiao-Xue-Yin)	Angelicae Radix 2.0 Cnidii Rhizoma 2.0 Rhemanniae Radix 2.0 Atractylodis Rhizoma 2.0 Hoelen 2.0 Aurantii Nobilis Pericarpium 2.0 Aconiti Tuber 2.0 Moutan Radix 2.0 Cyperi Rhizoma 2.0 Zizyphi Fructus 1.5 Zingiberis Siccatum Rhizoma 1.0 Glycyrrizae Radix 1.0 Leonuri Herba 1.5	Exhaustion, dysmenorrhea, neurosis after a delivery, weakness, pale face, palpitation, sleeplessness
Toki-shigyaku-ka-goshuyu-shokyo-to (Dang-Gui-Si-Ni-Jia-Wu-Zhu-Yü-Sheng-Jiang-Tang)	Zizyphi Fructus 5.0 Cinnamomi Cortex 3.0 Paeoniae Radix 3.0 Angelicae Radix 3.0 Akebiae Caulis 3.0 Glycyrrhizae Radix 2.0 Evodiae Fructus 2.0 Asiasari Radix 2.0 Zimgiberis Rhizoma 1.0	Cold hands and feet, pain in the limbs, pain in the lower abdomen, headache, weak patients, painful scars

*Indications show the target group according to the method of traditional herbal medicines.[10]

lobenzarit disodium (LD), and her polyarthralgia improved.

In 1987, the patient presented herself at our institution requesting treatment with traditional herbal (Kampo) medicine. We treated her with *Keishi-ni-eppi-itto-ka-ryojutsubu* (Gui-Zhi-Er-Yue-Bi-Yi-Tang-Jia-Ling-Zhu-Fu, 桂枝二越婢一湯加苓朮附), *Kyuki-choketsu-in* (Xong-Gui-Tiao-Xue-Yin, 芎帰調血飲) or *Toki-shigyaku-ka-goshuyushokyo-to* (Dang-Gui-Si-Ni-Jia-Wu-Zhu-Yü-Sheng-Jiang-Tang, 当帰四逆加呉茱萸生姜湯) (Table I) in addition to PSL and LZ. Kampo treatment resulted in a decrease in the serum inflammatory reaction as well as arthralgia. Thus, in December of that year, we discontinued LD and reduced the dosage of PSL from 10 mg/day to 7.5 mg/alternative day. Thus, in June 1988, PSL was discontinued. Subsequently, arthralgia was localized to the right elbow joint, and C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) remained low (CRP 0.3-0.5 mg/dl, ESR 8-25 mm/hour).

In January 1993, the patient gave birth. In June of that year, she suffered from bilateral wrist pain again, and subsequently experienced bilateral gonalgia. By June 1994, morning stiffness lasted about ten minutes, grip strength was 180 mmHg on the right and 210 mmHg on the left, and joint counts were 32 points.[14] Lansbury activity index[15] was 35 % and her status of RA was stage II, Class 2 at that time. There were no abnormal findings in the chest or abdomen. Her laboratory findings are shown in Table II. The CRP and ESR levels increased from her baseline and anti-nuclear antibody (ANA) was present. We considered her condition to represent progression of RA disease activity, and she was treated with Kampo formula, *Hochu-ekki-to,* which was selected according to the diagnostic method of traditional herbal medicine.[13] The selection of this formula was based on her general malaise and geographic tongue, suggesting a KI deficiency. Before administration of this formula, we treated her with *Toki-shakuyaku-san* (Dang-Gui-Shao-Yao-San, 当帰芍薬散), but the serum concentration of CRP had increased. Figure 1 shows the patient's clinical course. Kampo formula *Hochu-ekki-to* resulted in improvement in her symptoms, and her serum CRP was 1.0 mg/dl and ESR 36 mm/Hour in November 1994. RAHA titer changed from 640x to 320x in September although its titer remained 640x before September. As of June 1994, she had not taken any DMARDs.

To investigate the immune status of this patient, we measured the serum concentrations of soluble CD23 (sCD23) and TNF-α by antibody sandwich enzyme-linked immunosorbent assays (ELISA) using commercial kits (sCD23: T-cell Diagnostics, Inc.,

Table II Laboratory findings in June 1994

WBC	10340 /mm³	LDH	143 IU/L		
Neut	72.1 %	GOT	15 KU	ESR	51 mm/hr
Eos	1.2 %	GPT	11 KU	CRP	2.5 mg/dl
Baso	1.1 %	γ-GTP	14 IU/L	IgG	2056 mg/dl
Lymph	18.5 %	ALP	236 IU/L	IgM	275.8 mg/dl
Mono	5.7 %	T-BIL	0.4 mg/dl	IgA	467.6 mg/dl
RBC	460×10⁴/mm³	CH-E	0.84 ΔpH	RAHA§	640 ×
Hb	9.9 g/dl	T-Cho	180 mg/dl	ANA*	160 (Sp)×
PLT	48.4×10⁴/mm³	TG	91 mg/dl	CH_{50}	43 U/ml
TP	8.0 g/dl	Na	139 mEq/L	aDNA ab**	negative
Alb	4.1 g/dl	K	3.8 mEq/L	aSS-A/Ro ab#	negative
Alb	55.1 %	Cl	105 mEq/L	aSS-B/Ro ab	negative
α_1-glb	3.3 %	BUN	6 mg/dl		
α_2-glb	8.9 %	Cr	0.4 mg/dl	Urinalysis	WNL
β-glb	10.7 %	UA	2.8 mg/dl	Chest X-ray	WNL
γ-glb	21.6 %				

*Anti-nuclear antibody **anti-DNA antibody #anti SS-A/Ro antibody
§rheumatoid arthritis hemagglutination

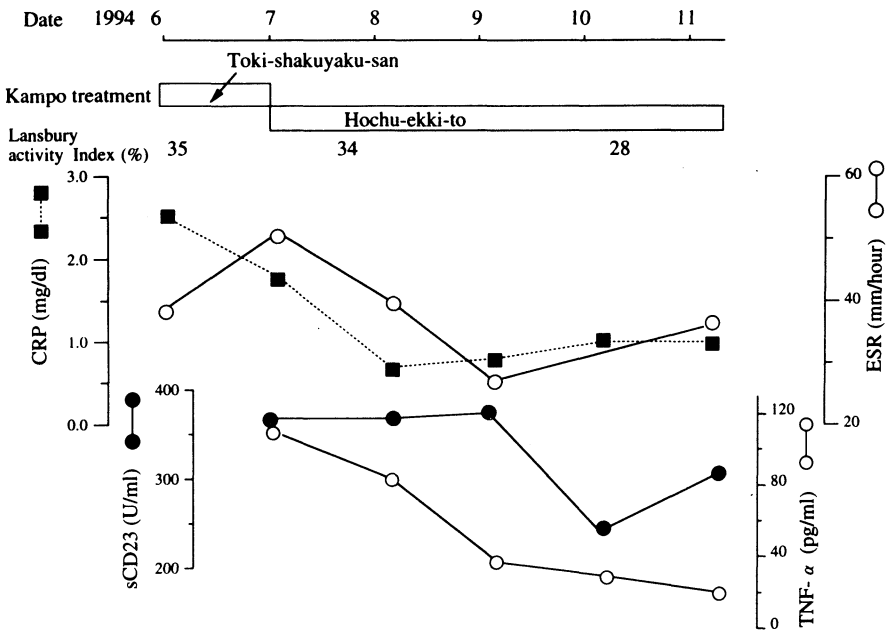

Figure 1 Clinical course and serological data after June 1994. Kampo treatment resulted in a decrease in symptoms, and her serum CRP was 1.0 mg/dl and ESR 36 mm/Hour in November 1994. The serum concentration of sCD23 remained high until September 1994, but its concentration decreased in October. Serum TNF-α concentration gradually decreased after the administration of Hochu-ekki-to. The finding from healthy subjects ; sCD23 : 63.4±21.5 U/ ml, TNF-α : 17.4±8.6 pg/ml, respectively. TNF-α : Tumor necrosis factor-α, CRP : C-reactive protein, ESR : Erythrocyte sedimentation rate.

Cambridge, MA ; TNF-α : Boehringer Mannheim Biochemica, Germany). sCD23 was expressed in U/ml, and TNF-α in pg/ml. The detection limits were 15 U/ml and 10 pg/ml for sCD23 and TNF-α, respectively. As a control, sera from 20 healthy volunteers were used. Serum samples were stored at -20°C until use. The finding from healthy subjects were ; sCD23 : 63.4 ±21.5 U/ml, and TNF-α : 17.4±8.6 pg/ml. As shown in Fig. 1, the patient's sCD23 concentration changed from 365 U/ml in July to 237 U/ml in October 1994. After that, the concentration remained in the 280-300 U/ml range. Serum TNF-α concentration gradually decreased after the administration of *Hochu-ekki-to*. Its concentration changed from 108 pg/ml to 18.5 pg/ml.

Discussion

Since the beginning of the 20th century, Western medicine has made rapid progress and many patients have been able to escape from pain. However, it is a fact that not all patients are satisfied with Western medicine. In Japan, about one-third of RA patients take alternative medicines.[16]

There are high expectations concerning the efficacy of these agents in the treatment of RA in Japan. These treatments are excellent in terms of safety, based on their use over thousands of years, and they may be administered continuously over several years. Many RA patients in Japan have been treated effectively with Kampo formulae.[17] In our previous study we demonstrated the effectiveness of *Keishi-ni-eppi-itto-ka-ryojutsubu* for RA by open trial.[1] Additionally, the action of Kampo formula or single herb is also being clarified.[2-7] However, whether there are changes in the immune status during treatment with herbal medicine for RA has not been established, although anti-inflammatory effects have been studied *in vitro*. Thus, in the present case study, we investigated the state of the immune system during Kampo treatment for RA.

For this patient, *Hochu-ekki-to* was effective in treating arthralgia by decreasing the levels of the classic inflammatory parameters—CRP and ESR. The

serum concentration of sCD23 remaind high untill September 1994, but its concentration decreased in October (Fig. 1). The change in sCD23 concentration was similar to that of RAHA titer, but not CRP concentration. CD23 molecule is expressed by peripheral blood B lymphocytes and several lymphoblastoid B cell lines.[18] This molecule was expressed at high levels by Epstein-Barr virus-transformed cells, and has thus been regarded as a B cell activation marker.[19] This surface antigen is continuously cleaved into soluble fragments, which are called soluble CD23.[20] Clinicaly, serum levels of sCD23 are elevated in primary Sjögren's syndrome, systemic lupus erythematosus and RA, and are correlated with the levels of IgM-RF in patients with RA.[9-11] Thus, sCD23 molecule is suitable for evaluating the immune status of RA patients. In the present case the serum concentration of sCD23 decreased, suggesting that Kampo treatment might suppress B cell activation in parallel with the anti-inflammatory effect. Recently, it has been domonstrated that sCD23 molecule enhances the interferon-γ-induced release of TNF-α from monocytes.[12] Thus, we also measured the serum concentration of TNF-α, and as shown in Fig. 1, its concentration also decreased. These findings suggest that this Kampo formula has anti-inflammatory effects and immunomodulatory effects, including suppression of B cell activation. Non-steroidal anti-inflammatory drugs (NSAIDs) did not suppress the production of IgG and IgA from peripheral blood mononuclear cells,[21] indicating that the actions of Kampo formulae do not equal those of NSAIDs.

We found a decrease in serum sCD23 concentration in a patient with RA and concluded that part of the therapeutic effect might be dependent on the suppression of B cell activation. We have not performed *in vitro* analyses such as those done on lobenzarit or bucilamine.[22,23] The reason for this is that a Kampo formula is a crude drug, and it is possible that unknown ingredients are contained in a water extract, therefore, such components may not always be absorbed into the intestine. In other words, it can not be ruled out that the action recognized in *in vitro* analysis results from an ingredient that is not detected in peripheral blood. Thus, it is important to clinically evaluate the immune status of the patient.

Finally, this is the first evaluation of changes in immune status during Kampo treatment. Kampo therapy resulted in a decrease in serum sCD23 concentration, as well as a decrease in RA disease activity, suggesting that its therapeutic effect might be attributable to suppression of B cell activation.

Supplementary notes

All Kampo formulae used for this patient were hot water extracts that were prepared from a mixture of several dried traditional herbal medicines. The mixture of dried herbal medicines was mixed in 600 ml of water and reduced to 300 ml. The aqueous extract, called the "decoction", was taken 3 times a day before meals. The components and indications for each Kampo formula are summarized in Table I.

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和文抄録

和漢薬治療は慢性関節リウマチ (RA) に対して極めて有用な治療法であるが，その作用機序に関しては，In Vitroによる生薬の抗炎症効果は解析されているものの，In Vivoでの免疫学的な評価はいまだ未着手な部分が多い。われわれは補中益気湯などが有効であったRAの一例を経験した。この患者は，RAの疾患活動性の低下に加えて血清中可溶性CD23 (sCD23) が低下し，さらに，血清TNF-α濃度も，漸次低下していた。このことからRAの治療において和漢薬は単に抗炎症効果を有するだけでなくImmunomodulatorとして作用している可能性が示唆された。その一部としてRA患者でのB細胞の活性化を抑制している可能性がある。

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