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A case of rheumatoid arthritis complicated by bucillamine-induced nephropathy satisfactorily treated with Kampo medicines

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Abstract

We reported a case of rheumatoid arthritis complicated by bucillamine-induced nephropathy satisfactorily treated with Kampo (Chinese/Japanese traditional) medicines. The patient was a 56-year-old male, who suffered from polyarthralgia from December 1996. In February 1997, he was diagnosed with RA in another hospital and treated with loxoprofen sodium, bucillamine and prednisolone. He visited our hospital in May 1997, and we began to treat him with a combination of modern Western and Kampo medicines. During his clinical course, proteinuria induced by bucillamine developed. After bucillamine was discontinued, his polyarthralgia and inflammatory parameters became worse. However, Kampo formulations, Keishi-bukuryo-gan mixed with Toki-shakuyaku-san and Dai-bofu-to, were effective for reducing the activity of RA. The clinical course of this case suggests that Kampo medicines might be useful for the treatment of RA patients, especially for those who have adverse reaction to disease-modifying antirheumatic drugs (DMARDs).

Key words rheumatoid arthritis, Kampo medicines, bucillamine nephropathy, Keishi-bukuryo-gan, Toki-shakuyaku-san, Dai-bofu-to.

Abbreviations RA, rheumatoid arthritis ; NSAIDs, nonsteroidal antiinflammatory drugs ; DMARDs, disease modifying antirheumatic drugs ; Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan), (桂枝茯苓丸) ; Toki-shakuyaku-san (Dang-Gui-Shao-Yao-San), (当帰芍薬散) ; Dai-bofu-to (Da-Fang-Feng-Tang), (大防風湯) ; Keishi-ka-ryo-jutsu-bu-to (Gui-Zhi-Jia-Ling-Zhu-Fu-Tang), (桂枝加苓朮附湯) ; Ogi (Huang-Qi), (黄耆), Astragali Radix, *Astragalus membranaceus* BUNGE; Keishi-ni-eppi-ichi-to (Gui-Zhi-Er-Yue-Bi-Yi-Tang), (桂枝二越婢一湯) ; Sojutsu (Cang-Zhu), (蒼朮), Atractylodis Lanceae Rhizoma, *Atractylodes lancea* DE CANDOLLE ; Boi (Fang-Ji), (防已), Sinomeni Caulis et Rhizoma, *Sinomenium acutum* REHDER et WILSON ; Yokuinin-to (Yi-Yi-Ren-Tang), (薏苡仁湯) ; Keishi-shakuyaku-chimo-to (Gui-Zhi-Shao-Yao-Zhi-Mu-Tang), (桂枝芍薬知母湯) ; Gosha-jinki-gan (Niu-Che-Shen-Qi-Wan), (牛車腎気丸) ; Kekkyo (Xue-Xu), (血虚), *deficiency of blood*; Oketsu (Yu-Xue), (瘀血), *blood stasis* ; Suitai (Shui-Zhi), (水滞), *stasis of body fluid* ; Kikyo (Qi-Xu), (気虚), *deficiency of vital energy* ; In (Yin), (陰) ; Yo (Yang), (陽) ; Kyo (Xu), (虚), *deficiency* ; Jitsu (Shi), (実), *excess*.

Introduction

In modern Western medicine, essential medicinal treatment for rheumatoid arthritis (RA) is based on nonsteroidal antiinflammatory drugs (NSAIDs) and disease modifying antirheumatic drugs (DMARDs), and corticosteroid is sometimes used. In Japan, bucillamine, one of the DMARDs, is often used, but this agent is prone to cause adverse reactions such as

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eruption,[1] renal dysfunction,[2,3] interstitial pneumonia,[4] agranulocytosis,[5] and so on. The renal dysfunction induced by bucillamine is called bucillamine-induced nephropathy and this complication is suspected by the development of proteinuria. In this paper, we report on a case of rheumatoid arthritis complicated by bucillamine nephropathy, to whom it was difficult to administer DMARDs, satisfactorily treated with Kampo (Chinese/Japanese traditional) medicines.

Case report

The patient was a 56-year-old man who had no medical history or records of his family. In December 1996, he suffered from arthralgia of the bilateral shoulders. In January 1997, arthralgia occurred in the bilateral fingers, wrists and knees followed by morning stiffness. In February, he consulted a doctor in another hospital and was diagnosed as having rheumatoid arthritis (RA). His C-reactive protein (CRP) was 4.5 mg/dl and erythrocyte sedimentation rate (ESR) was 87 mm/1hr. He was administered loxoprofen sodium at 180 mg/day and bucillamine at 200 mg/day. In March, however, CRP increased to 10.3 mg/dl, so he was treated with prednisolone at 20 mg/day for 3 days, 15 mg/day for 4 days, 10 mg/day for 7 days, then 5 mg/day. However, he continued to complain about severe arthralgia.

He visited our hospital in May 1997. He complained of arthralgia of the bilateral shoulders, wrists, fingers, knees and ankles. Physical examination revealed a height of 164 cm and a weight of 50 kg. His body temperature was 35.7°C, pulse 72/min and regular, and blood pressure 130/78 mmHg. There was no edema or eruption of the skin, but the bilateral metacarpophalangeal joints of the index fingers and the left knee joint were swollen. The conjunctivas were not anemic or icteric, and tonsils and thyroid were not swollen. On auscultation, heart sounds were normal and no murmur was heard. The liver, spleen and kidneys were not palpable. There was no neurological abnormality.

His initial laboratory data in our hospital are shown in Table I. On May 13, 1997, ESR (104 mm/1hr), CRP (2.5 mg/dl) and rheumatoid factor (RF: 1,157 IU/ml) were elevated. Anti-nuclear antibody (ANA: ×40, nucleolar type) was positive. Finger-bone X-ray showed mild erosion and osteoporosis. There were no abnormalities in chest X-ray, electrocardiogram, abdominal ultrasonography or upper gastrointestinal fiberscopy. From the total of these findings, we diagnosed him as having RA, functional stage II, anatomical class II.[6,7] His joint count was 118 and the Lansbury's index was 73 on May 13.[8]

Initial findings based on the concept of Kampo medicine were as follows. Subjective symptoms: easy fatigability, lack of will power, loss of appetite, feeling of heaviness in the whole body, swelling and stiffness of the finger joints, swelling of the legs. Pulse: pulsus superficialis, frequens and intentus. Tongue: dark red, purple and livid color of the tongue body, thick and white-yellow fur. Abdomen: slightly

Table I Initial laboratory data in our hospital (May 13, 1997).

WBC	7,490 /μl	TP	7.0 g/dl	T-Chol	99 mg/dl
RBC	421 ×10⁴/μl	alb	50.9 %	TG	58 mg/dl
Hb	12.8 g/dl	α1-gl	4.0 %	BUN	12 mg/dl
Ht	39.7 %	α2-gl	12.1 %	Cr	0.6 mg/dl
Plt	37.7 ×10⁴/μl	β-gl	14.6 %	UA	4.5 mg/dl
		γ-gl	18.4 %	Na	141 mEq/l
ESR	104 mm/hr	LDH	157 IU/l	K	4.2 mEq/l
CRP	2.5 mg/dl	AST	20 IU/l	Cl	104 mEq/l
RF	1,157 IU/ml	ALT	17 IU/l	FBS	88 mg/dl
ANA	×40 (NU)	γ-GTP	47 IU/l	Urinalysis	
CH50	39 U/ml	Alp	218 IU/l	protein	±
C3	103.7 mg/dl	T-Bil	0.3 mg/dl	oc. blood	±
C4	18.6 mg/dl	CPK	58 IU/l	glucose	−

decreased abdominal tension, hypertonic rectus abdominis muscle, reduced abdominal tension in the lower abdomen.

His clinical course is shown in Fig. 1. We continued to administer loxoprofen at 180 mg/day, bucillamine at 200 mg/day and prednisolone at 5 mg/day, and added a Kampo prescription, Keishi-ka-ryo-jutsu-bu-to with Ogi (5 g). As this prescription was not so effective and he complained of thirst, we changed it to Keishi-ni-eppi-ichi-to with Sojutsu (5 g) and Boi (5 g) in June. Boi administered to this patient was not *Aristolochia fanchi* WU but *Sinomenium acutum* REHDER et WILSON. Also in June, proteinuria appeared. We considered the possibility that loxoprofen might have negatively affected his kidneys, so we changed to sulindac at 300 mg/day. Proteinuria then disappeared, but skin eruption developed. We considered that this eruption was drug-induced, so we changed the NSAID from sulindac to 25 mg/day of diclofenac sodium, and we discontinued the administration of bucillamine at the same time. His skin eruption disappeared soon, but thereafter, ESR, CRP, joint count and Lansbury's index were aggravated. We administered bucillamine again in July. From the efficacy of bucillamine, we considered that the activity of RA was markedly improved.

In December 1997, proteinuria appeared again. We considered this to be an adverse reaction of bucillamine, the so-called bucillamine nephropathy, and ceased its administration. Thereafter, the activity of RA became aggravated, and his skin became dry and rough, this meant Kekkyo (*deficiency of blood*), so we changed the Kampo prescription to Yokuinin-to and then to Keishi-shakuyaku-chimo-to with Boi (5 g) and Ogi (5 g), but they were not effective. Proteinuria continued and polyarthralgia was still severe, so we changed the NSAID from diclofenac to loxoprofen at 60 mg/day in March 1998. At the same time, we changed the Kampo prescription from Keishi-shakuyaku-chimo-to with Boi and Ogi to Keishi-bukuryo-gan mixed with Toki-shakuyaku-san because a sign of Oketsu (*blood stasis*), resistance tender on pressure of para-umbilical region, and a sign of Suitai (*stasis of body fluid*), swelling of the

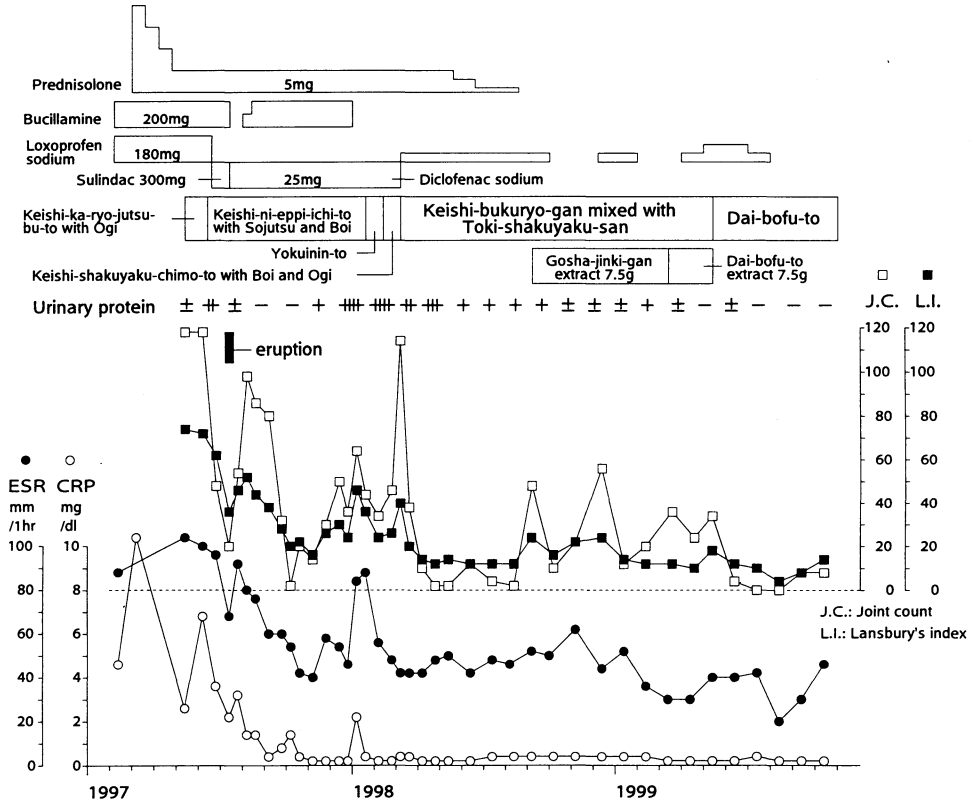

Fig. 1 Clinical course.

legs, appeared. The joint count and Lansbury's index decreased remarkably and urinary protein also declined. In August, we withdrew the administration of prednisolone. In September, because he complained of arthralgia of the bilateral metatarsophalangeal joints, and swelling of legs and reduced lower abdominal tension existed, we added Gosha-jinki-gan extract at 7.5 g/day. As Gosha-jinki-gan extract was not so effective and he complained of fatigue and muscle cramp, we diagnosed him as Kikyo and Kekkyo (*deficiency both of vital energy and blood*), changed this to Dai-bofu-to extract at 7.5 g/day in March 1999. This prescription was slightly effective for his arthralgia, so we administered it as a decoction and discontinued Keishi-bukuryo-gan mixed with Toki-shakuyaku-san in May. Thereafter, polyarthralgia improved remarkably and urinary protein was eliminated.

Discussion

We treated this RA patient with a combination therapy of modern Western and Kampo medicines. In this case, bucillamine, one of the DMARDs, was effective for reducing the activity of RA, but proteinuria developed during its use. Bucillamine-induced membranous nephropathy is a known clinical entity.[2,3] It was reported that after suspending the further use of bucillamine, proteinuria would gradually reduce to be eliminated within 10 months without specific treatment or without increases in the dose of corticosteroid.[3] In our case as well, proteinuria was eliminated after the cessation of bucillamine.

In the present case, however, after stopping the use of bucillamine, the activity of RA became exacerbated. We hesitated to administer another kind of DMARD because of the possibility of adverse effects, so we tried to reduce the RA activity with Kampo medicines. From the concepts of Kampo medicine, he was diagnosed in the clinical course as following. Oketsu, a blood stagnation syndrome; because of the dark skin color and livid lips, gingiva and tongue, and resistance tender on pressure of para-umbilical region. Kekkyo, a blood deficiency syndrome; because of the dry and rough skin, hypertonic rectus abdominis muscle and muscle cramp. Suitai, a body fluid stasis syndrome; because of swelling and stiffness of joints and swelling of legs. Kikyo, a vital energy deficiency syndrome; because of general physical fatigue, lack of will power and loss of appetite.[9]

In this case, Keishi-bukuryo-gan mixed with Toki-shakuyaku-san and Dai-bofu-to (Table II) were effective for improving RA after the suspension of bucillamine. The former prescription is the combination of Keishi-bukuryo-gan and Toki-shakuyaku-san, both of which are used for the treatment of

Table II Crude drugs of prescriptions mainly used in this case.

Prescription	Keishi-bukuryo-gan mixed with Toki-shakuyaku-san (Gui-Zhi-Fu-Ling-Wan mixed with Dang-Gui-Shao-Yao-San)
Crude drugs (g/day)	Cinnamomi Cortex* 4.0, Hoelen*# 5.0, Moutan Cortex* 4.0, Persicae Semen* 4.0, Paeoniae Radix*# 5.0, Alismatis Rhizoma# 6.0, Atractylodis Rhizoma# 4.0, Cnidii Rhizoma# 3.0, Angelicae Radix# 3.0
Prescription	Dai-bofu-to (Da-Fang-Feng-Tang)
Crude drugs (g/day)	Angelicae Radix 3.0, Paeoniae Radix 3.0, Rehmanniae Radix 3.0, Astragali Radix 3.0, Saposhnikoviae Radix 3.0, Eucommiae Cortex 3.0, Atractylodis Rhizoma 3.0, Cnidii Rhizoma 2.0, Ginseng Radix 1.5, Notopterygii Rhizoma 1.5, Achyranthis Radix 1.5, Glycyrrhizae Radix 1.5, Zizyphi Fructus 1.5, Zingiberis Siccatum Rhizoma 1.0, Aconiti Tuber 2.0

Keishi-bukuryo-gan mixed with Toki-shakuyaku-san was decocted in 600ml of boiling water for 30-40 minutes and reduced to 300 ml. Dai-bofu-to was decocted in 800 ml of boiling water for 50-60 minutes and reduced to 300 ml. The decoction was taken 3 times a day.
*: Crude drugs composing in Keishi-bukuryo-gan. #: Crude drugs composing in Toki-shakuyaku-san.

Oketsu, and the latter is also used for Kekkyo and Suitai.[10] According to the concept of Kampo Medicine, Keishi-bukuryo-gan should be administered to a patient in Yo and Jitsu state and Toki-shakuyaku-san to a patient in In and Kyo state. Therefore, these two prescriptions are not commonly combined. We dared to try to administer Keishi-bukuryo-gan mixed with Toki-shakuyaku-san to the patient because of his severe Oketsu state and moderate Kekkyo and Suitai state. Thereafter, we administered Dai-bofu-to to him because of his condition of Kikyo and Kekkyo.[10] There were case reports noting that Toki-shakuyaku-san and Dai-bofu-to were effective in the treatment of RA.[11,12] It was also reported that the severity of Oketsu was significantly correlated with the activity of RA, assessed by Lansbury's index, and that these two parameters had a tendency to change in parallel.[13] These findings suggest the possibility that the treatment for Oketsu leads to improvement of the activity of RA.

In conclusion, the present case report suggests that Kampo medicines might be useful for the treatment of RA patients, especially for those who have adverse reactions to DMARDs and must avoid them.

和文抄録

ブシラミン腎症を併発した慢性関節リウマチ(RA)に対して，漢方治療が奏功した1例を報告した。症例は56歳，男性。1996年12月，多関節痛出現。1997年2月，他院にてRAの診断のもと，ロキソプロフェン，プレドニゾロン，ブシラミンにて加療を受けた。1997年5月，当科初診以来，現代西洋医学的治療に漢方治療を併用して加療にあたった。経過中，ブシラミンによる蛋白尿が出現。ブシラミンを中止したところ，多関節痛と炎症反応が悪化した。しかし，桂枝茯苓丸合当帰芍薬散および大防風湯が奏功し，RAの活動性が低下し蛋白尿も消失した。このことから，副作用によりDMARDsが使用困難なRAの治療に対して，漢方治療が有効である可能性が示唆された。

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