

CASE REPORT

Toshiaki Kogure · Ayami Hoshino · Katsuhiko Ito
Hiroko Sato · Takeshi Tatsumi · Yasuo Ohyama
Etsuo Kawata · Kin'ichi Fujita · Jun'ichi Tamura

Beneficial effect of complementary alternative medicine on lymphedema with rheumatoid arthritis

Received: July 19, 2005 / Accepted: October 11, 2005

Abstract Lymphedema of the limbs can be an added complication in a small number of rheumatoid arthritis cases, becoming a long-standing problem even when there is good control of inflammatory joint disease. In the present article, we describe a patient with RA who developed lymphedema of the forearms successfully treated with TJ-48 (Juzentaihoto) as a complementary alternative medicine (CAM). This kind of edema does not seem to show any consistent relationship with the severity of arthritis in the literature surveyed. In contrast, lymphedema in this case improved in parallel with RA disease activity. We discuss the utility of CAM treatments and review the literature.

Key words Complementary alternative medicine (CAM) · Juzentaihoto · Lymphedema · Rheumatoid arthritis (RA)

Introduction

Lymphedema is a well recognized but rare complication of rheumatoid arthritis (RA), first described in 1968.¹ Swelling of the hand and distal forearm in inflammatory arthritis is commonly due to joint synovitis or tenosynovitis. In contrast, lymphedema involves either increased capillary filtration or impaired lymphatic drainage.² Since this kind of edema does not show any consistent relationship to the duration or severity of arthritis,^{3–5} it is often difficult to improve lymphedema with disease-modifying antirheumatic drugs (DMARDs), corticosteroids, or methotrexate (MTX).

In Japan, traditional herbal medicines as complementary alternative medicine (CAM) play an important role in the field of primary health care, and 147 Kampo formulae are covered by the National Health Insurance Scheme. Clinical and immunomodulatory effects of several Kampo formulae have been demonstrated in both experimental mice^{6,7} with arthritis and patients with RA.^{8,9}

Described herein is a patient with chronic seropositive RA complicated by rheumatoid lymphedema, who was prescribed Juzentaihoto (TJ-48) in March 2003 after failure to respond to corticosteroid and DMARDs. She demonstrated a dramatic improvement in arthritis as well as lymphedema.

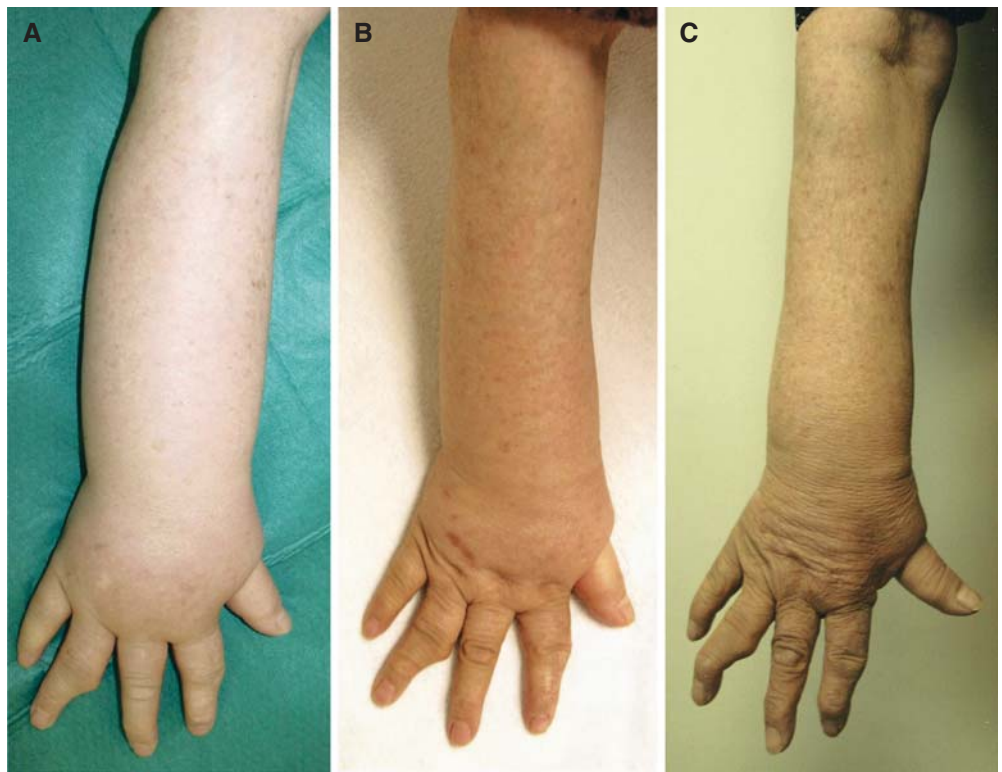
Case report

The patient consulted our hospital in March 2003 at 67 years of age, with bilateral upper limb lymphedema associated with RA. In 1977, she developed pain and swelling of the bilateral wrist joints and was diagnosed as having RA at a local hospital. Although she was treated with loxoprofen sodium 180mg/day, gold sodium thiomalate (GST) 20mg biweekly, salazosulfapyridine 500mg/day, and prednisolone (PSL) 2.5mg/day, joint destruction worsened. Polyarthralgia persisted and bilateral upper limb lymphedema appeared in 1999. Thereafter, she consulted our hospital with a request for alternative medicine. At the first medical examination in March 2003, she had slight pain and severe deformity of the bilateral hands, and pitting edema in the upper extremities with no evidence of vascular compromise (Fig. 1A). There was no warmth or erythema. There were no significant findings on physical examination of the neck, chest, and abdomen. There were no breast masses, adenopathy or skin change, or edema at bilateral lower extremities. The duration of morning stiffness was 60min, and the score of joint count¹⁰ was 96 points. Laboratory data were as follows: hemoglobin (Hb) 12.6g/dl, erythrocyte sedimentation rate (ESR) 37mm/h, C-reactive protein (CRP) 1.5mg/dl, IgG 1280mg/dl, IgA 579mg/dl, IgM

T. Kogure (✉) · K. Ito · H. Sato · T. Tatsumi
Department of Integrated Japanese Oriental Medicine, School of
Medicine, Gunma University, 3-39-22 Showa-machi, Maebashi
371-8511, Japan
Tel./Fax +81-27-220-8666
e-mail: tkogure@showa.gunma-u.ac.jp

A. Hoshino · Y. Ohyama · E. Kawata · K. Fujita · J. Tamura
Department of General Practice Medicine, Graduate School of
Medicine, Gunma University, Maebashi, Japan

Fig. 1. **A** Right arm with lymphedema on the first examination (in March 2003) at our hospital. There was no redness or warmth. The edema existed in the arm as well as hand or wrist. **B,C** Lymphedema improved remarkably after treatment with TJ-48. **B** In February 2004. **C** In December 2004



186 mg/dl, rheumatoid factor (RF) 27 IU/ml, antinuclear antibody (ANA) 1:40 (homogeneous pattern). Hepatic, renal and thyroid function was normal. There was no hypoalbuminemia or proteinuria during the disease course. RS₃PE syndrome was denied by the viewpoint of positive RF, destruction of joints, and long duration.¹¹ She was clinically diagnosed as having lymphedema accompanying RA. Activities of daily living, especially handwork, showed marked deterioration due to diffuse bilateral wrist and forearm swelling, although polyarthralgia was within tolerable limits.

In March 2003, Juzentaihoto (TJ-48; Tsumura, Tokyo, Japan) was prescribed at 7.5 g (oral) daily. At that time, GST and loxoprofen sodium were discontinued. Within 8 weeks her synovitis improved, and by 12 weeks lymphedema was dramatically reduced. In February 2004, PSL was also discontinued. Except for some residual tightness and swelling of the palm and dorsum of the hand, swelling of the forearm up to the elbow had virtually resolved (Fig. 1A–C). In December 2004, ESR, CRP, and RF were 17 mm/h, 0.1 mg/dl, and 10 IU/ml. Subsequently, her condition entered remission after treatment with TJ-48 (Fig. 2).

Discussion

Rheumatoid lymphedema is an uncommon extra-articular feature of RA. Previously reported patients are listed in Table 1. One of three patients reported by Grillet and

Dequeker³ was excluded because diffuse swelling of the left arm was probably induced by local inflammation. The majority of previous reports described lymphedema as persistent. Lymphedema under such circumstances is thought to be due to the development of inflammation and possible fibrosis of the superficial lymph vessels as complications of synovitis, with subsequent obstruction of lymphatic flow due to lymph node swelling, etc.^{2,4,5,12,13} However, it has been reported that some of the patients did not show any correlation between severity of lymphatic impairment and duration or severity of arthritis,^{4,5} suggesting that local factors other than lymphatic function may influence the threshold below which edema occurs. Casley-Smith and Piller have reported that lymphedema was partially derived from the failure of macrophages to absorb protein in the tissue fluid.¹⁴ It is thought that lymphedema in RA is attributed to both the obstruction of lymphatic flow and impaired absorption of excessive protein by macrophages. In general, lymph node swelling is usually related to disease activity of RA; however, the ability of macrophages to absorb protein is not associated with immune status.¹⁵ Therefore, the appearance of lymphedema may not show a correlation with disease activity in RA.

Treatment is usually symptomatic, with application of pressure stockings and, in rare instances, surgery. These approaches have been only partially successful. Medical management of RA has not been of consistent benefit for lymphedema, and in the majority of patients, it is a longstanding problem even with good control of the underlying inflammatory joint disease.^{4,5,16} This is the first case report

Table 1. List of patients with lymphedema associated with rheumatoid arthritis

First author, year ^{Ref.}	Age/sex	Site of LE	Onset of LE after RA	RF	ANA	Therapy	Outcome	
							RA	LE
Grillet, 1987 ³	52/M	Hands, ankle	<1	(-)	ND	GST, penicillamine, corticosteroids	Partially controlled	Improvement
Grillet, 1987 ³	46/M	Hands	3	(-)	ND	GST, chloroquine, methyl-PSL pulse therapy	Improvement	Improvement
Dacre, 1990 ⁴	57/M	Hands	<1	(-)	(-)	Indomethacin	Improvement	Minor improvement
Dacre, 1990 ⁴	52/M	Hands	8	(+)	(-)	SASP, PSL, CPA, gold	Minor improvement	Minor improvement
Dacre, 1990 ⁴	44/M	Hands	1	(+)	(+)	NSAIDs	Minor improvement	Persistent
Dacre, 1990 ⁴	51/F	Hands	<2	(-)	(+)	Auranofin	Improvement	Persistent
Dacre, 1990 ⁴	45/F	Hands	2	(+)	ND	Azathioprine	Not described	Persistent
Dacre, 1990 ⁴	62/M	Hands	5	(-)	(-)	NSAIDs	Improvement	Persistent
Dacre, 1990 ⁴	54/F	Feet	<1	(+)	(-)	NSAIDs, penicillamine, chlorambucil	Persistent	Persistent
Kiely, 1994 ⁵	40/F	Hands	2	(+)	ND	Gold, SASP, penicillamine	Relative remission	Persistent
Kiely, 1994 ⁵	75/M	Hands	9	(-)	ND	NSAIDs, gold	Mildly controlled	Persistent
Kiely, 1994 ⁵	38/F	Hands	15	(-)	ND	Penicillamine	Partially controlled	Persistent
Salvarani, 1995 ¹⁶	ND	Hand	ND	ND	ND	DMARDs, AI of corticosteroids	Unknown	Persistent
Salvarani, 1995 ¹⁶	ND	Hands	ND	ND	ND	DMARDs, AI of corticosteroids	Unknown	Persistent
Ostrov, 2001 ¹⁷	58/F	Hands	3	(+)	(-)	NSAIDs, PSL, MTX, etanercept	Improvement	Improvement
Present case	67/F	Hands	20	(+)	(+)	NSAIDs, PSL, SASP, TJ-48	Improvement	Improvement

LE, lymphedema; RA, rheumatoid arthritis; RF, rheumatoid factor; ANA, antinuclear antibody; GST, gold sodium thiomalate; SASP, salazosulfapyridine; PSL, prednisolone; CPA, cyclophosphamide; MTX, methotrexate; AI, articular injection; NSAIDs, nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs

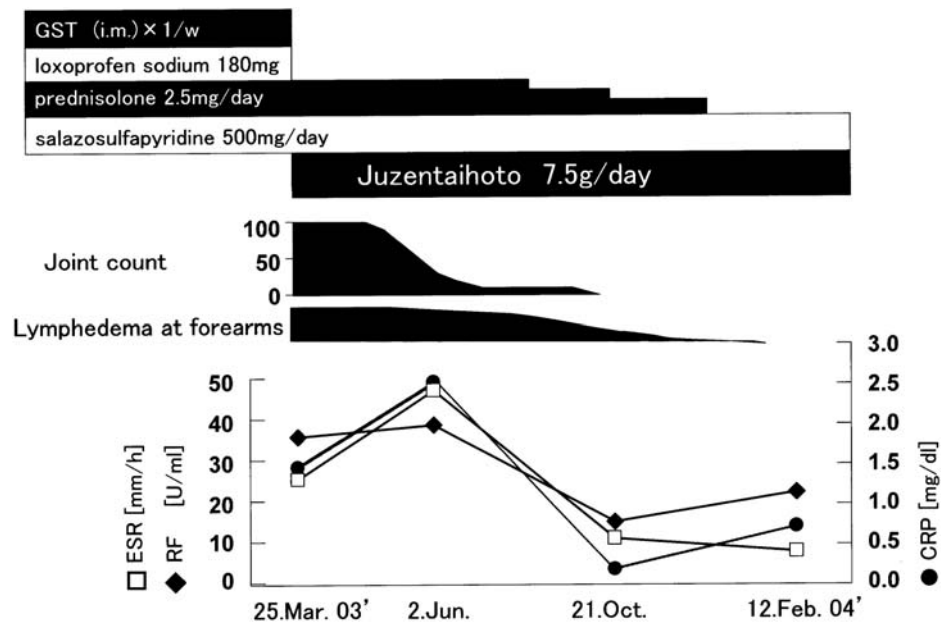
demonstrating the beneficial effect of Juzentaihoto, a traditional herbal medicine, on rheumatoid lymphedema. Recently, it was reported that anti-tumor necrosis factor (TNF) therapy, etanercept, was useful for the treatment of lymphedema,¹⁷ though the present case did not fulfill the indications for anti-TNF therapy in Japan. Additionally, the efficacy of infliximab was reported for lymphedema associated with ankylosing spondylitis.¹⁸

Juzentaihoto/TJ-48, a traditional herbal medicine, has previously been used to treat patients with anemia, anorexia, or fatigue.^{19,20} In the field of traditional medicine, it is now considered that the advanced stage of RA is also a good indication for Juzentaihoto.²¹ The indications for usage in RA patients are thought to be: (i) over 5 years after onset; (ii) advanced stage of joint deformity; (iii) fatigue, loss of appetite, dry skin, and anemia; and (iv) easy susceptibility or amyloidosis. Previous studies have shown that TJ-48 has various biological activities: enhancement of

phagocytosis,²² cytokine induction,^{23,24} and antibody production,²⁵ and an inhibitory effect on tumor progression or metastasis.^{26,27} Recently, we reported that TJ-48 enhanced the expression of inducible nitric oxide synthase (iNOS) in an lipopolysaccharide (LPS)-activated murine macrophage cell line,²⁸ and upregulated the expression of killer-cell immunoglobulin-like receptors (KIRs) on peripheral lymphocytes.²⁹ Although Juzentaihoto possesses immunomodulatory effects as described above, the mechanism for RA and immune status in the target group is still not clear.

Hochuekkito, which has tonic effects that are similar to those of Juzentaihoto in traditional medicine, induced an improvement in type II collagen (CII)-induced arthritis (CIA) in DBA1J mice as well as suppressing anti-CII antibody production and interleukin-6 release.⁷ Based on this finding, we speculate that Juzentaihoto also improves arthritis by suppressing B-cell activation similar to

Fig. 2. Clinical course. Rheumatoid arthritis, disease activity, erythrocyte sedimentation rate (*ESR*), serum level of C-reactive protein (*CRP*), rheumatoid factor (*RF*), and joint count improved along with lymphedema. *GST*, gold sodium thiomalate



hochuekkito. Importantly, there is another problem, namely in our case that the treatment of TJ-48 resulted in the improvement of disease activity as well as lymphedema of the upper limbs. Juzentaihoto might possess immunomodulatory effects and increase the ability of macrophage to absorb protein. In fact, it has been shown that TJ-48 enhances phagocytosis²² as well as expression of iNOS in an LPS-activated murine macrophage cell line.²⁸ Thus, it is considered that these mechanisms may be involved in the improvement of both disease activity and lymphedema in our case.

In summary, we reported a patient with RA who developed lymphedema of the forearms and was successfully treated with Juzentaihoto/TJ-48. This kind of edema does not seem to show any consistent relationship with the severity of arthritis according to the literature, although the lymphedema improved in parallel with RA disease activity in our case. The development of lymphedema may be associated with various causes, and Juzentaihoto may possess several actions that treat refractory lymphedema accompanying RA.

References

- Kalliomaki JL, Vastamaki M. Chronic diffuse edema of the rheumatoid hand. A sign of local lymphatic involvement. *Ann Rheum Dis* 1968;27:167-9.
- Kiely PDW, Bland JM, Joseph AEA, Mortimer PS, Bourke BE. Upper limb lymphatic function in inflammatory arthritis. *J Rheumatol* 1995;22:214-7.
- Grillet B, Dequeker J. Rheumatoid lymphedema. *J Rheumatol* 1987;14:1095-7.
- Dacre JE, Scott DL, Huskisson EC. Lymphoedema of the limbs as an extra-articular feature of rheumatoid arthritis. *Ann Rheum Dis* 1990;49:722-4.
- Kiely PDW, Joseph AEA, Mortimer PS, Bourke BE. Upper limb lymphoedema associated with polyarthritis of rheumatoid type. *J Rheumatol* 1994;21:1043-5.
- Niizawa A, Kogure T, Hai le X, Fujinaga H, Takahashi K, Shimada Y, et al. Clinical and immunomodulatory effects of fun-boi, an herbal medicine, on collagen-induced arthritis in vivo. *Clin Exp Rheumatol* 2003;21:57-62.
- Hai le X, Kogure T, Niizawa A, Fujinaga H, Sakakibara I, Shimada Y, et al. Suppressive effect of hochu-ekki-to on collagen induced arthritis in DBA1J mice. *J Rheumatol* 2002;29:1601-8.
- Niizawa A, Kogure T, Fujinaga H, Takahashi K, Shimada Y, Terasawa K. Clinical and immunomodulatory effect of fun-boi, an herbal medicine, in rheumatoid arthritis. *J Clin Rheumatol* 2000;6:244-9.
- Kogure T, Itoh T, Shimada Y, Takahashi K, Terasawa K. The influence of a traditional herbal medicine on the disease activity in patients with rheumatoid arthritis. *Clin Rheumatol Relat Res* 1996;8:233-41.
- Kotaniemi A, Isomaki H, Hakala M, Risteli L, Risteli J. Increased Type I collagen degradation in early rheumatoid arthritis. *J Rheumatol* 1994;21:1593-6.
- Sano M, Okamoto S, Yamawaki T, Sakauchi M, Meguro T, Takita T, Narushima K, Suzuki N. Two cases of RS3PE syndrome (in Japanese). *Ryemachi* 1997;37:493-8.
- Mulherin DM, Fitzgerald O, Bresnihan B. Lymphedema of the upper limb in patients with psoriatic arthritis. *Semin Arthritis Rheum* 1993;22:350-6.
- Thornbury KD, McHale NG, Allen JM, Hughes G. Nerve-mediated contractions of sheep mesenteric lymph node capsules. *J Physiol* 1990;422:513-22.
- Casley-Smith JR, Piller N. The mode of action of coumarin and related compounds in the treatment of edema. In: Clodius L, editor. *Lymphedema*. Stuttgart: Georg Thieme; 1977. p. 33-41.
- Bruns RR, Palade GE. Studies on blood capillaries. II. Transport of ferritin molecules across the wall of muscle capillaries. *J Cell Biol* 1968;37:277-99.
- Salvarani C. Upper limb lymphoedema in inflammatory arthropathy. *J Rheumatol* 1995;22:370.
- Ostrov BE. Beneficial effect of etanercept on rheumatoid lymphedema. *Arthritis Rheum* 2001;44:240-1.
- Almodovar R, Zarco P, Quiros FJ, Mazzucchelli R. Infliximab treatment efficacy in lymphoedema associated with ankylosing spondylitis. *Rheumatology* 2004;43:1456.
- Terasawa K. Introduction. In: *KAMPO Japanese-Oriental medicine; insights from clinical cases*. Tokyo: KK Standard McIntyre; 1993. p. 1-13.
- Takahashi K, Terasawa K, Shimada T, Mitsuma T, Imadaya A. A case of rheumatoid arthritis successfully treated with juzentaihoto (in Japanese). *Kampo Med* 1992;42:43-7.

21. Kogure T. Bu Ji (Hozai): Kampo therapy for RA by decoction (in Japanese). *Ryumachika* 2002;27:499–507.
22. Maruyama H, Kawamura H, Takemoto N, Komatsu Y, Aburada M, Hosoya E. Effect of Juzen-taiho-to on phagocytosis (in Japanese). *Jpn J Inflamm* 1998;8:461–5.
23. Haranaka K, Satomi N, Sakurai A, Haranaka R, Okada N, Kobayashi M. Antitumor activities and tumor necrosis factor producibility of traditional Chinese medicines and crude drugs. *Cancer Immunol Immunother* 1985;20:1–5.
24. Kubota A, Okamura S, Shimoda K, Harada N, Omori F, Niho Y. A traditional Chinese herbal medicine, juzen-taiho-to, augments the production of granulocyte/macrophage colony-stimulating factor from human peripheral blood mononuclear cells in vitro. *Int J Immunother* 1992;8:191–5.
25. Hamada M, Fujii Y, Yamamoto H, Miyazawa Y, Shui SM, Tung YC, et al. Effect of a kampo medicine, zyuzentaihoto, on the immune reactivity of tumor-bearing mice. *J Ethnopharma* 1988;24:311–20.
26. Ohnishi Y, Fujii H, Kimura F, Mishima T, Murata J, Tazawa K, et al. Inhibitory effect of a traditional Chinese medicine, Juzen-taiho-to, on progressive growth of weakly malignant clone cells derived from murine fibrosarcoma. *Jpn J Cancer Res* 1996;87:1039–44.
27. Ohnishi Y, Fujii H, Hayakawa Y, Sakukawa R, Yamaura T, Sakamoto T, et al. Oral administration of a Kampo (Japanese herbal) medicine Juzen-taiho-to inhibits liver metastasis of colon 26-L5 carcinoma cells. *Jpn J Cancer Res* 1998;89:206–13.
28. Kawamata H, Ochiai H, Mantani N, Terasawa K. Enhanced expression of inducible nitric oxide synthase by juzen-taiho-to in LPS-activated RAW264.7 cells, a murine macrophage cell line. *Am J Chinese Med* 2000;28:217–26.
29. Kogure T, Itoh K, Tatsumi T, Sekiya S, Sakai S, Shimada Y, et al. The effect of juzentaihoto/TJ-48 on the expression of killer-cell immunoglobulin-like receptors (CD158a/b) on peripheral lymphocytes: in vitro experiment. *Phytomedicine* 2005;12:327–32.