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**DOPPLER SONOGRAPHIC ANALYSIS OF SYNOVIAL VASCULARIZATION  
IN A PATIENT WITH RHEUMATOID ARTHRITIS TREATED  
WITH LEUKOCYTAPHERESIS**

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**Abstract** : Synovial vascularization in metacarpophalangeal joints of a patient with rheumatoid arthritis treated with leukocytapheresis (LCAP) was evaluated by Doppler sonography. After the treatment with LCAP, evaluation with American College of Rheumatology core set showed improvement, and the levels of C-reactive protein and serum amyloid A protein decreased. Power Doppler sonography demonstrated a reduction of color flow signals of the joints, and spectral Doppler sonography demonstrated an increase in vascular resistance, indicating a reduction of vessel's permeability. This is the first report evaluating a synovial vascularization and blood flow of the joints by Doppler sonography before and after LCAP therapy. Doppler sonography might be one of the useful methods for evaluating the therapeutic response of LCAP.

**Key words** : Doppler sonography, Leukocytapheresis (LCAP), Rheumatoid arthritis, Synovial vascularization, Vascular resistance

INTRODUCTION

Leukocytapheresis (LCAP) is one of the therapies for rheumatoid arthritis (RA) by removing activated white blood cells from patient's peripheral blood. Several mechanisms of LCAP have been proposed, however, there are no reports evaluating an effect of LCAP to synovial vascularity. Pulse-waved spectral Doppler sonography can demonstrate increased vascularization and decreased vascular resistance in the inflammatory synovium, which allows evaluating arthritis quantitatively and

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associates with clinical disease activity of RA.

In this report, we describe a patient with RA in whom we evaluated synovial vascularization and blood flow on metacarpophalangeal (MCP) joints by Doppler sonography before and after the treatment with LCAP.

#### CASE REPORT

The patient was a 49-year-old woman with a 25-year history of RA. She received bilateral total knee and hip arthroplasty because of severe deformity of those joints. She had been treated with methotrexate, salazosulfapyridine, and prednisolone. In January 2003, a renal biopsy was performed, and histological examination revealed secondary renal amyloidosis and interstitial nephritis. Additionally, a chest computed tomography (CT) revealed interstitial pneumonia. Consequently, methotrexate and salazosulfapyridine were discontinued and only prednisolone was continued. One month after, the arthralgia aggravated and laboratory tests revealed increased C-reactive protein (CRP) and serum amyloid A protein (SAA). She was hospitalized for a treatment with LCAP in April 2005.

Upon admission, her body temperature was 37.5°C. Fine crackles were heard from the dorsal side of the lower regions of lungs. Twenty-six joints including all of MCP joints were swelling. Her functional status was classified as class III according to the revised American College of Rheumatology (ACR) classification.

Laboratory tests revealed positive CRP at the level of 2.3 mg/dl and high white blood cell count of 9,200/ $\mu$ l. The levels of blood urea nitrogen (25 mg/dl) and creatinine (2.1 mg/dl) were high, and urinary protein was 0.65 g/day. The levels of rheumatoid factor (399 IU/ml), matrix metalloproteinase-3 (708 ng/ml), and SAA (52.4  $\mu$ g/ml) were all high.

Chest X-ray and computed tomography showed reticular shadows in the middle and lower fields of both lungs. Bone X-ray indicated deformities, dislocations, and bony ankylosis in the proximal interphalangeal joints, MCP joints, and wrists. The case was classified as stage IV according to the Steinbrocker classification. Cervical radiography showed exceeded preodontoid space (6 mm), indicating an atlantoaxial subluxation.

She did not receive disease-modifying anti-rheumatic drugs because of interstitial pneumonia and renal disorder. Therefore, LCAP using Cellsorba® (Asahi Medical Co. Ltd., Tokyo, Japan) was performed once a week, five times in total. Therapeutic effects were evaluated using the ACR core sets<sup>1)</sup>, CRP, SAA, and synovial vascularization on MCP joints by Doppler sonography before and after the treatment with LCAP.

Doppler sonography was performed using a LOGIQ7 system (GE Medical Systems, USA). Color flow signals and vascular resistance (resistance index [RI]) were evaluated using methods described in a previous report<sup>2)</sup>. Briefly, a multidimensional linear scanner 546L (GE Medical Systems, USA) at a power setting

of 5.0 MHz was used as the transducer. MCP joints of the second to fifth fingers of the right hand were scanned longitudinally and transversely on the dorsal side of the joints. Power Doppler was performed using standard methods with a pulse repetition frequency, 9.8 to 10.2 kHz. The intensity of vascularization in the joints was evaluated by counting the number of color flow signals using grades established in a modification of Klauser's method<sup>3)</sup>: grade 0, no color flow signal; grade 1, 1 to 4 color flow signals; grade 2, 5 to 8 color flow signals; grade 3, 9 or more color flow signals. Mean values of color flow signals were calculated as the mean grades of sonographic images with positive color flow signals, out of the total of eight sonographic images (longitudinal and transverse) obtained for each set of four MCP joints.

One of the color flow signals obtained by power Doppler sonography was randomly selected, and was examined for pulse waves by spectral Doppler sonography. The marginal edge of a pulse wave in a spectral Doppler sonogram was traced with a dotted line (as shown figure C, D). Then, the RI was calculated using a computer and the following formulas;  $RI = \text{peak systolic (maximum) velocity} - \text{end diastolic (minimum) velocity} / \text{peak systolic (maximum) velocity}$ . Mean RI was calculated as the mean RI values of sonographic images with positive velocity waves, out of the total of eight sonographic images obtained for each set of four MCP joints.

After the treatment with LCAP, evaluation with the ACR core set showed ACR20 improvement, and the levels of CRP and SAA decreased (Table 1). Mean color flow signals of the MCP joints also improved from grade 2 to 1. RI rose from 0.73 to 0.81, indicating a reduction of vessels' permeability. Representative power Doppler and spectral Doppler sonographic images are shown in the Fig. 1.

Table 1. Evaluations before and after LCAP

	Before	After
Tender joint count	5	0
Swollen joint count	26	14
Patient's assessment of pain	6	2
Patient's global assessment of disease activity	6	2
Physician's global assessment of disease activity	5	2
Patient's global assessment of physical function (HAQ-DI)	2.125	2.000
CRP (mg/dl)	2.3	0.9
SAA ( $\mu\text{g/ml}$ )	52.4	37.7
Grade of color flow signals	2	1
Vascular resistance (RI)	0.73	0.81

LCAP=Leukocytapheresis

SAA=Serum Amyloid A protein

HAQ-DI=Health Assessment Questionnaire-Diasability Index

RI=Resistance Index

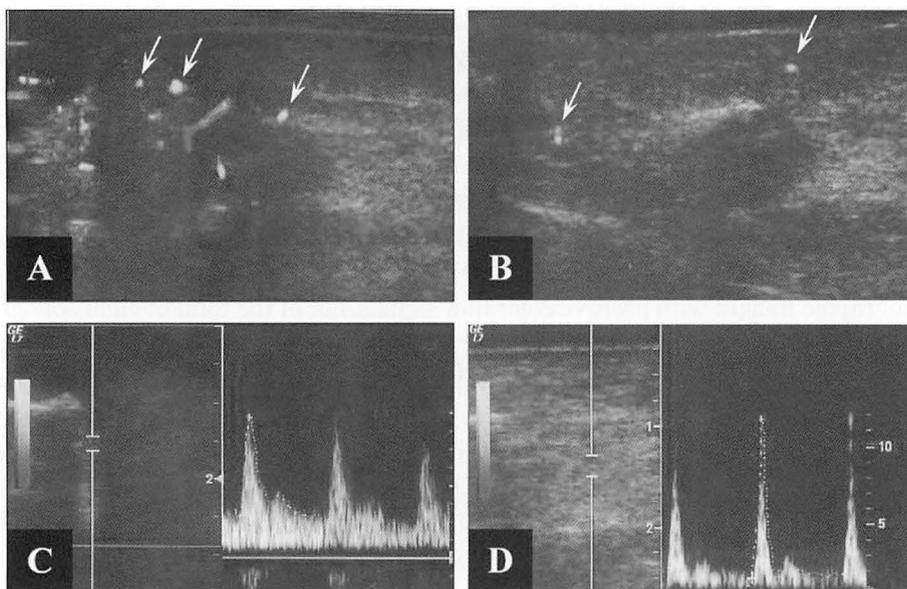


Fig. 1. Power Doppler images in the MCP joints before (A) and after (B) the LCAP therapy. Spectral Doppler images in the MCP joints before (C) and after (D) the LCAP therapy. Color flow signals (arrows) decreased from grade 2 (A) to grade 1 (B). The resistance index (RI) increased from 0.73 to 0.81.

#### DISCUSSION

This is the first report describing a treatment with the LCAP resulted in a reduction of color flow signals and an increase of vascular resistance associated with an improvement of ACR20 in a case of RA. The conventional tools for imaging joints are radiography and magnetic resonance (MR). Radiography shows bone erosion. MR imaging has been shown to be more sensitive than radiography, and contrast material-enhanced MR imaging allows early identification of inflammatory process such as synovitis, effusion, and tenosynovitis. However, the assessment of multiple joints with MR imaging is not common because MR imaging is too expensive and not available at bedside. In contrast, Doppler sonography has recently been reported to be useful for at bedside imaging arthritis because of an improved accuracy of sonographic devices<sup>2-5</sup>). Interestingly, there are several reports that Doppler sonography clearly showed decreased color flow signals and increased RI in the synovium of patients with RA after anti-tumor necrosis factor- $\alpha$  therapy<sup>6-13</sup>).

LCAP absorbs the white blood cell during a continuous extracorporeal circulation using a hemoperfusion column packed with fine-diameter fibers of polyethylene terephthalate. In each apheresis procedure, a total of 2,000 to 3,000 ml of blood is processed at the rate of 50 ml/minute in 1 hour. It is performed once a week, and repeated five times in all. The therapy is indicated to patients with RA in whom the disease is highly active, resistant to medications, or rapidly aggravating, and the

condition meets two or more of the following criteria : swollen joint count is 6 or more ; blood sedimentation rate is 50 mm in 1 hour or higher ; or CRP is 3 mg/dl or higher. The advantage of LCAP therapy is that it can be indicated to patients with multiple complications because adverse events rarely occur compared to the other therapies<sup>14</sup>).

The efficacy of LCAP has been reported ACR20 improvement in 64% to 79%, and ACR50 improvement in 16% to 27% of RA patients<sup>14-16</sup>). Although LCAP therapy has been shown to be clinically effective, its mechanism remains largely unknown. Mechanisms of LCAP are suggested as follows ; removal of the activated white blood, alteration of the cytokine balance, removal of the activated platelets, and transfer of the activated white blood cells from inflammatory joints to peripheral blood<sup>14,17,18</sup>). This case indicates that an improvement of synovial vascularization might also be one of the mechanisms of LCAP.

This case was difficult to be treated with disease-modifying anti-rheumatic drugs because of complications, but the symptoms were improved after the LCAP therapy. This results show that LCAP can be a safe and effective therapy in patients with RA who have multiple complications. There are many cases in which LCAP does not affect to the level of CRP or erythrocyte sedimentation rate even though it relieves arthralgia and joint swelling. Doppler sonography might be one of the useful methods for evaluating the therapeutic response of LCAP as shown in this case. Further studies with large numbers of patients are desirable.

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