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ORIGINAL ARTICLE

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Assessment of inflamed synovial membrane in the knee joint by dynamic magnetic resonance imaging

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Abstract Dynamic magnetic resonance imaging (dynamic MRI) was used to examine the synovial membrane in the knee joints of 15 patients with rheumatoid arthritis (RA) in order to investigate the relationship between pathological and MRI findings. Signal intensities in the regions of interest (ROI), identified as the synovial membrane of the suprapatellar pouch, were measured on MR images. Signal intensities at various times after the injection of contrast medium Gd–diethylenetriaminopentoacetic acid (Gd–DTPA) were normalized relative to the signal intensity at 80 s, and designated as the normalized signal intensity (NSI). Pathological findings were quantified, and the types of inflamed synovial membrane were classified as either acute or chronic. A significant difference in NSI was observed between acute and chronic types ($P < 0.05$). Dynamic MRI was capable of classifying acute and chronic RA by measuring NSI 20 s after contrast medium injection. Dynamic MRI was therefore shown to be useful for assessing regional synovial inflammation.

Key words Dynamic magnetic resonance imaging (Dynamic MRI) · Gd-diethylenetriaminopentoacetic acid (Gd–DTPA) · Normalized signal intensity (NSI) · Rheumatoid arthritis (RA) · Suprapatellar pouch

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Introduction

To overcome the difficulties of assessing the local activity of arthritis in patients with rheumatoid arthritis (RA),[1] techniques using magnetic resonance imaging (MRI) are currently being investigated. MRI using the contrast medium Gd–diethylenetriaminopentoacetic acid (Gd–DTPA) is reported to be particularly useful for assessing inflammation of the synovial membranes.[2–5] Several recent reports have also documented the effectiveness of dynamic MRI for assessing inflamed synovial membranes.[6–12] However, a reliable assessment technique based on dynamic MRI has not yet been established. In this study, we attempted to assess inflammatory activity in the articular synovial membrane of RA patients using dynamic MRI. Dynamic MRI is expected to offer a measure of synovial inflammatory activity owing to rapid enhancement soon after contrast medium injection. On the other hand, pathological assessment by biopsy offers information on synovial inflammatory activity, and allows the classification of RA into acute and chronic types. We first investigated the relationship between pathological and dynamic MRI findings, and then determined useful criteria in the dynamic MRI findings for classifying the two types of RA. Finally, we ascertained whether dynamic MRI was practical for evaluating RA.

Subjects

The subjects were 15 patients (2 male, 13 female) who were diagnosed as having RA at the Department of Orthopedic Surgery of Kitasato University Hospital according to the criteria established by the American College of Rheumatology (ACR). The patients' ages ranged from 32 to 72 years (mean 59 years), and their disease duration ranged from 1 to 31 years (mean 11 years). Between 1999 and 2000, MRI was performed 1 week before patients underwent total knee arthroplasty (TKA).

Methods

Dynamic MRI was performed using the Signa LX (1.5T, GE Medical Systems, Milwaukee, WI, USA) under the following conditions: pulse sequence, gradient echo; TR/TE, 10.6/1.5 ms; flip angle, 20°; field of view, 20 cm. MR images were obtained at 0, 20, 40, 60, 80, and 100 s after rapid intravenous injection of contrast medium (Gd–DTPA). Imaging started when the contrast medium entered the vessel (0 s), and 10 ml of the contrast medium was injected at 1 ml/s. In this study, 5-mm-thick sagittal images, including the center of the patella, were analyzed (Fig. 1). The signal intensity (SI) on each sagittal image was measured in the upper central region of the suprapatellar pouch (SI(n), where n = time after contrast medium injection). The size of the region measured was determined by the degree of synovial proliferation (white circular region; indicated by the arrow in Fig. 1). The average diameter of the region was 5 mm. Signal intensities at various times after the injection of contrast medium were normalized relative to the signal intensity at 80 s, and were referred to as the normalized signal intensity (NSI).

$$\mathrm{NSI}(n) = \{\mathrm{SI}(n) - \mathrm{SI}(0)\}/\{\mathrm{SI}(80) - \mathrm{SI}(0)\}$$

In this study, the reference time point was set at the moment when the signal intensity began to increase. Because NSI values below 0.1 were omitted, the reference point was set at 20 s after injection in three patients. As a result, NSI was determined up to 80 s in all 15 patients.

For pathological investigations, the synovial membrane of the suprapatellar pouch, obtained during TKA, was fixed in 10% neutral formaldehyde and stained using hematoxylin–eosin (H&E). These synovial membrane specimens were examined according to the method of Tamai et al.,[9,13] and the following elements were assessed: 1, neovascularization; 2, layering of superficial cells; 3, lymphocyte infiltration; 4, fibroblast proliferation; 5, fibrosis. While elements 1, 2, and 3 are indicators of acute RA (acute index), 4 and 5 are indicators of chronic RA (chronic index). Each element was classified into four grades: 0, slight; 1, mild; 2, severe; 3, very severe. The acute index point was the sum of the grades for 1, 2, and 3, while the chronic index point was the sum of the grades for 4 and 5. Patients were diagnosed as having acute RA when the acute index point was 5 or more, or was higher than the chronic index point. All other patients were classified as having chronic RA (Table 1). In addition, levels of C-reactive protein (CRP) were measured by a blood test as an indicator of inflammation. For statistical analysis, Student's t-test was conducted, and a P-value of less than 0.05 was considered to be significant.

Results

Nine patients were diagnosed with acute RA and 6 patients with chronic RA. Figure 2 shows typical pathological find-

Table 1. Pathological assessment of the synovial membrane

Acute index	1. Neovascularization	Points:
	2. Layering of superficial cells	slight 0
	3. Lymphocyte infiltration	mild 1
		severe 2
Chronic index	4. Fibroblast proliferation	very severe 3
	5. Fibrosis	

Acute type means acute index points ≥ 5, or acute index points greater than chronic index points. Chronic type means everything except the above

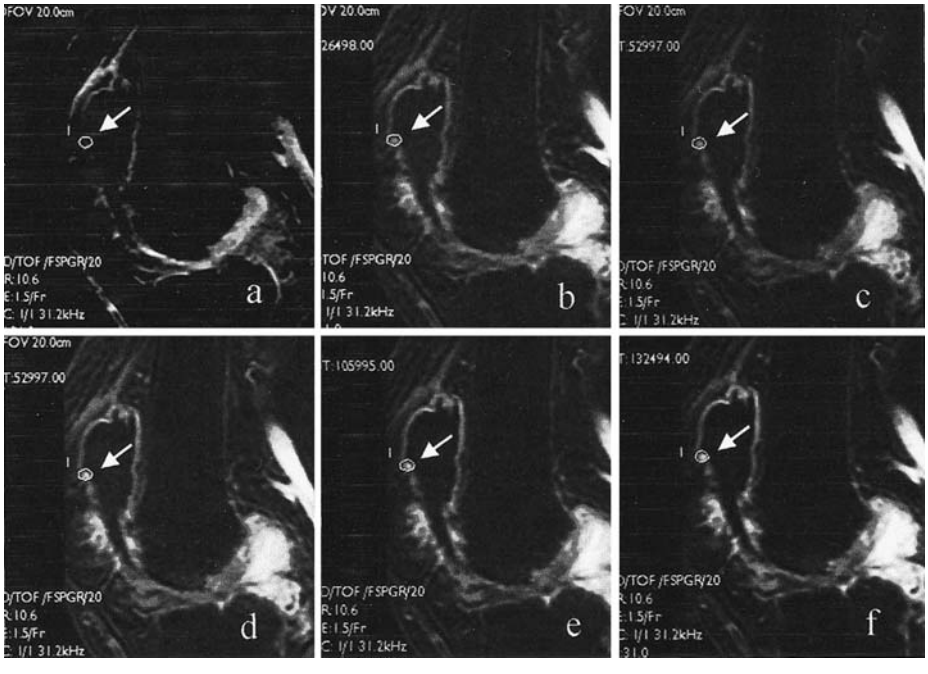

Fig. 1. Dynamic MRI findings in the knee joint. *White circles* indicated with *arrows* are regions of interest where signal intensities were measured. *a*, immediately after injection; *b*, 20 s after injection; *c*, 40 s after injection; *d*, 60 s after injection; *e*, 80 s after injection; *f*, 100 s after injection

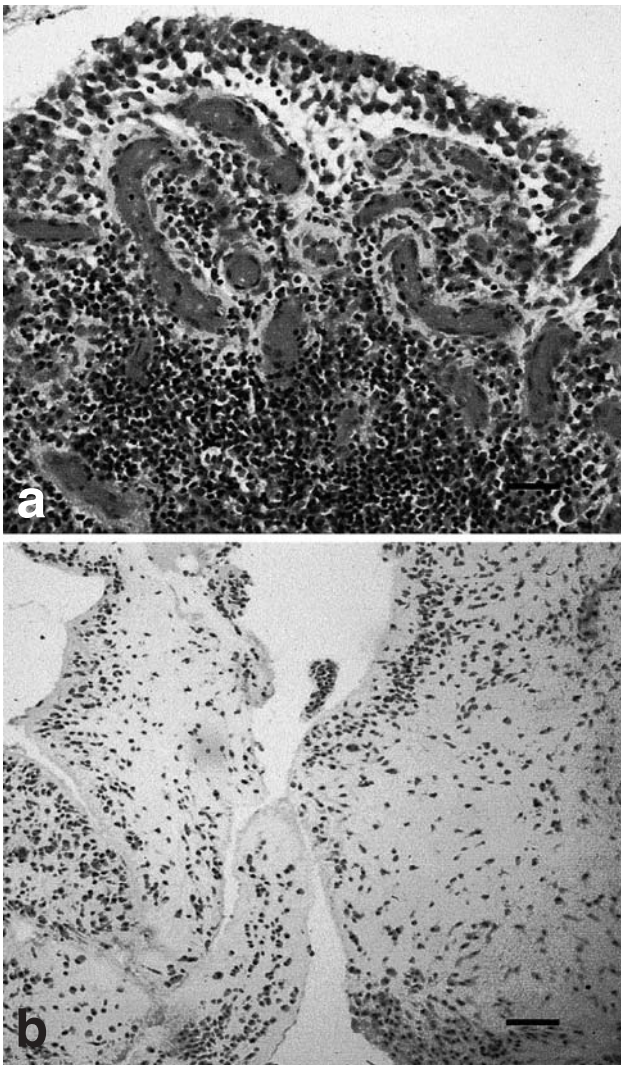

Fig. 2. Pathological findings of synovial membrane in the knee joint. **a** Acute type: neovascularization and significant lymphocyte infiltration can be seen (H&E, *bar* 100 μm). **b** Chronic type: remarkable fibrosis can be seen (H&E, *bar* 100 μm)

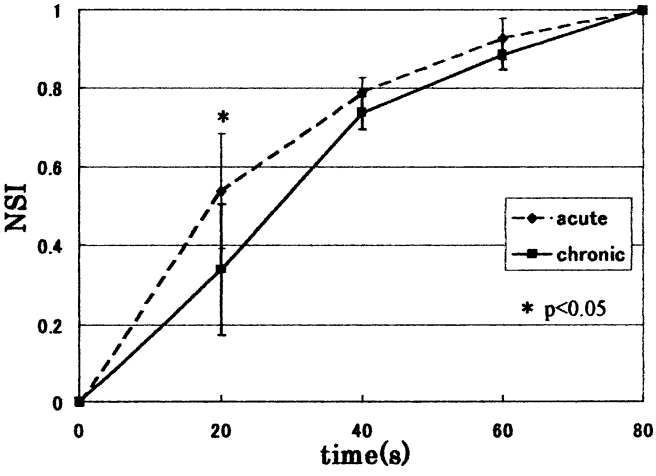

Fig. 3. Relationship between normalized signal intensity (*NSI*) (mean ± SD) and time after injection in acute and chronic RA

Discussion

Reiser et al.[12] first used dynamic MRI to assess articular synovial membranes in 1989. Gd–DTPA injected into a blood vessel is known to diffuse throughout the interstitial fluid, ultimately reaching the joint cavity via the synovial membrane. The diffusion of Gd–DTPA is affected by synovial blood flow and permeability, and thus changes in diffusion can indicate pathological changes in synovial membranes.[14,15] Tamai et al.[13] compared the results of dynamic MRI and those of pathological investigation for knee joints of RA patients, and reported that signal intensity was closely related to papillary proliferation, cellular infiltration, increased vascularization, and granulation, but was not related to intrasynovial fibrosis.

At present, there is no comprehensive histopathological method for assessing RA synovial membranes. Therefore, in this study, five findings associated with RA synovial membranes were divided into acute and chronic indexes in order to investigate differences in MRI signal intensity.

Figure 3 shows that the mean value of NSI(20) for acute RA was 0.553, while that for chronic RA (0.338) was lower by 0.215. A *t*-test revealed a significant difference between the two RA types ($P < 0.05$). However, no significant difference was seen at 40 s or later. Ostergaard et al.[6] reported that the optimal time for signal intensity measurement was 30–60 s after the administration of contrast medium. In this study, the maximum difference between acute and chronic RA was seen at 20 s after injection. One reason for this time discrepancy could be that the reference point was set at 20 s after contrast-medium injection in three of the patients. In these patients, poor hemodynamics were thought to have resulted in the delayed arrival of the contrast medium at the synovial membrane in the suprapatellar pouch. This may have shortened the maximum postadministration signal intensity. In addition, NSI can fluctuate depending on the injection rate or the volume of contrast medium, and it is therefore necessary to standardize these variables.

ings: Fig. 2a, neovascularization, significant lymphocyte infiltration, and layering of superficial cells as seen in acute RA cases; Fig. 2b, marked fibrosis as seen in chronic RA cases.

Figure 3 shows the results of dynamic MRI. The mean NSI value at 20 s was 0.553 for acute RA and 0.338 for chronic RA, at 40 s it was 0.783 and 0.738, respectively, and at 60 s it was 0.912 and 0.886, respectively. A significant difference was seen in the NSI at 20 s between acute and chronic RA patients ($P < 0.05$). However, no significant differences were observed between the two groups at 40 or 60 s.

The range of CRP in acute RA patients was 275–6139 μg/dl, and that in chronic RA patients was 412–5233 μg/dl. No clear correlation was demonstrated.

The average disease duration was 10 years for acute RA and 13 years for chronic RA, and no difference in RA activity with respect to disease duration was observed.

In this study, the patients were divided into two groups based on pathological findings (acute or chronic RA). In order to agree as closely as possible with the results of pathological findings using dynamic MRI, the cutoff value for NSI(20) was set at 0.55. Thus, acute RA was diagnosed when NSI(20) $\geq$ 0.55, and chronic RA was diagnosed when NSI(20) $<$ 0.55. Based on this criterion, two of the nine patients who were pathologically diagnosed as having acute RA would have been diagnosed as having chronic RA by dynamic MRI (NSI(20) = 0.24 and 0.43). This is probably due to the size of the regions examined with dynamic MRI. The average diameter of the regions examined was about 5 mm. Therefore, in patients with a thin synovial membrane, a higher volume of neighboring tissue (articular edemas and muscles) was examined with the synovial tissue, which probably caused errors in the signal intensity measurement.

Gaffney et al.[8] reported that chronological changes in the signal intensity from synovial membranes measured by dynamic MRI correlated with histological findings associated with acute inflammation, but not with blood tests or intraarticular pressure (IAP). In our study, the results using dynamic MRI demonstrated that the NSI value 20 s after contrast medium injection is useful for assessing regional articular inflammation in RA patients. Furthermore, based on MRI findings, patients with acute RA could be differentiated from those with chronic RA with comparable accuracy to differentiation based on the results of pathological investigation. However, patients with acute RA could not be differentiated from those with chronic RA based on the results of blood tests (CRP) or disease duration. Therefore, dynamic MRI should prove useful in assessing regional inflammation and therapeutic effectiveness in the knee joint as well as in other joints.[10,11,16,17]

Only 15 patients were enrolled in this study, and thus we need to conduct more studies involving more patients.

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