CLINICAL ARTICLE

Rheumatoid Arthritis of Knee Joints: MRI–Pathological Correlation

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Objective: To evaluate the correlation between features of knee joint rheumatoid arthritis (RA) identified on MRI and histological examination as a means of elucidating the pathogenesis of joint destruction in RA.

Methods: This is a prospective analysis of 26 knee joints of 22 patients who underwent total knee arthroplasty (TKA) for the treatment of RA. Based on the degree of destruction of articular cartilage and the menisci, the occurrence of bone marrow edema and bone erosion, and synovial thickening, the stage of the knee joints were classified using MRI by two radiologists. Differences in the severity of destruction of the articular cartilage of the medial and lateral femoral condyles and medial and lateral tibial plateaus, the medial and lateral menisci, and bone were compared using analysis of variance with a post-hoc test, and the Mann–Whitney *U*-test. Samples of cartilage, subchondral bone, menisci, and synovium were obtained from the resected knee specimens during TKA and analyzed semiquantitatively using microscopy and immunohistochemistry. Histological differences between areas of bone erosion and bone marrow edema were evaluated using a Mann–Whitney *U*-test.

Results: The extent of articular destruction was classified as grade 4 for the medial and lateral femoral condyles and the medial and lateral tibial plateaus for most patients, with an average destruction grade of 3.6 ($F = 5.455$, $P = 0.002$), with the least amount of destruction identified on the lateral femoral condyle. The majority of knee joints in the RA patients were at stage 3 (21/26, 80.8%), followed by stage 4 (4/26, 15.4%). Fibrosis, thinning and destruction, and hyperplasia were the most severe pathological changes in cartilage. In a total of 26 specimens, 36 areas of bone marrow edema and 68 areas of bone erosion were identified, with fibrosis, a mosaic structure of bone, and lymphocyte infiltration being the most severe changes in these areas. The degree of meniscus destruction was classified as grade 4 in the majority patients for both the medial and lateral meniscus, with an average degree of meniscal destruction over all specimens of 3.85, and greater destruction of the medial meniscus than of the lateral meniscus ($Z = 2.062$, $P = 0.039$). Fibrosis and engulfing calcified debris were the most severe pathological manifestations. Synovitis was also identified in all 26 specimens, with hyperplasia of intima cells and lymphocyte and plasma cell infiltration being the most severe pathological manifestations.

Conclusions: Severe destruction of the articular cartilage and menisci is a characteristic feature of RA. Bone marrow edema and bone erosion can both also be found, but are less characteristic. Synovial infiltration may be the triggering mechanism of the destruction of the cartilage, menisci, and bone marrow. However, the origin of bone marrow edema requires further investigation.

Key words: Immunohistochemistry; Knee joint; MRI; Pathology; Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease of unknown etiology that affects approximately 1% of the world population, with

approximately 50% of adults being unable to work within 10 years of disease onset^{1,2}. Although the pathogenesis of RA is not completely understood, the disease involves synovial joints and leads to progressive joint destruction³. The knee

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joint is commonly involved in RA. Aletaha *et al.* suggested that damage to the cartilage was more clearly associated with irreversible physical disability than the destruction to bone among patients with RA⁴. The meniscus also has important effects on the knee; however, few studies on RA focus on this tissue. Therefore, research of the destruction mechanisms of RA on joint cartilage and meniscus are clinically meaningful.

There was evidence of destruction of the articular cartilage of the femoral condyles appearing early in the disease process, including roughening, softening, and fibrillation⁵. Moreover, in their observation of the knee joint cartilage in 50 patients who underwent synovectomy in the course of RA disease, Chaplin observed areas of cartilage that were completely destroyed and usually filled with soft granulation tissue⁵. They further observed that the menisci in 25 of their cases had either disappeared completely or were less than half of their expected size. In their study of the knee joint in 47 patients who underwent synovectomy for RA treatment, Kimura and Vainio also concluded that the knee menisci underwent a more rapid process of degeneration than the cartilage, with a loss of elasticity, fraying, fasciculation, and atrophy⁶. Few histological studies have been performed to clarify the mechanisms underlying the early destruction of knee joint cartilage and menisci observed in interventional studies.

The mechanisms underlying the development of bone marrow edema and erosion in RA are debated. The leading hypothesis is that pannus, which is a hyperplastic synovium filled with inflammatory cells and dilated vessels, damages bone marrow, especially in bare areas that are uncovered by cartilage, with this effect on bone marrow resulting in bone destruction. Conaghan *et al.* support this view of synovitis as a primary cause of the pathogenesis of bone edema in early RA but do not agree with the concept of independent areas of destruction in bone⁷. Similarly, Schett *et al.* elaborated on the mechanism of synovial infiltration into the bone marrow in detail in their review on the mechanisms of joint destruction in RA⁸. In contrast, Jimenez-Boj *et al.* found that inflammatory infiltrates in the bone marrow were either isolated or found in contact with the synovium⁹. Similarly, Bugatti *et al.* observed the simultaneous presence of some lymphoid aggregates and osteoclasts in deep areas of the bone marrow, at sites distant from apparent synovial invasion, without excluding the possibility of an independent inflammatory process of the subchondral bone in RA¹⁰. Furthermore, McQueen and Ostendorf identified separate foci of lymphoid cells in areas of bone marrow edema, which were remote from the bare area observed in the cartilage¹¹. Therefore, the origin of bone marrow edema and bone erosion in RA is an issue under discussion.

MRI is considered to be the best non-invasive observer-independent modality to evaluate RA, and provides an opportunity to identify inflammatory lesions that are not detectable on standard clinical examination³. In their MRI study of knee joint RA, using a 1.5T MR scanner, Poleksic *et al.* identified synovial thickening, including inflammatory

and fibrous proliferation, joint effusion, marginal erosions and subchondral cysts, periarticular soft tissue swelling, popliteal cysts, and tendon thickening as RA features of the knee joint, with all presenting with abnormally high signal intensity (SI)¹². Based on their MRI study of the knee joint in RA, Forney *et al.* reported synovitis, edema-like bone marrow, and bone erosion to be the three major intra-articular MRI findings of RA, and of other forms of inflammatory arthritis¹³. However, studies conducted to date have not provided a detailed examination of MRI manifestations of knee joint RA, including an assessment of the correlation between MRI findings and histological findings.

Therefore, the purpose of our study was to correlate MRI manifestations of knee joint RA (including the articular cartilage, subchondral bone, meniscus, and synovium) with histological findings, and to discuss plausible mechanisms underlying the destruction of the articular cartilage and the meniscus, and whether the bone marrow edema and bone erosion in RA have the same pathological features. We hypothesized that inflammatory infiltrates in one tissue could lead to destruction in other tissues of the knee joint in RA.

Materials and Methods

Our study was approved by our institutional ethics committee and conforms to the provisions of the Declaration of Helsinki. All patients provided informed consent.

Inclusion and Exclusion Criteria

Between November 2013 and October 2016, all patients who fulfilled the American College of Rheumatology (formerly, the American Rheumatism Association) criteria for RA¹⁴ and were scheduled for total knee arthroplasty (TKA) for RA treatment were enrolled into the study. The indications for TKA included chronic and persistent pain, joint swelling, and functional restriction in knee joint range of motion. Patients with contraindications to MRI, prior knee surgery, trauma, inflammation, metabolic diseases, and other diseases around the knee were excluded.

MRI Protocols

All the patients performed MR examinations either with a 0.35T (Magnetom C, Siemens Medical Solutions, Erlangen, Germany) scanner or with a 3T MRI (MR750, GE Healthcare, Milwaukee, WI, USA) scanner. The patients were placed in a supine position, with the knee extended. The sagittal T1-weighted spoiled gradient echo (SPGR) sequence, the sagittal short time of inversion recovery (STIR) proton density weighted imaging (PDWI) sequence, the coronal STIR PDWI sequence, and the traverse STIR T2 weighted imaging (WI) sequence were used.

Magnetic Resonance-based Classifications and Definitions

The degree of articular cartilage destruction on the medial femoral condyle, lateral femoral condyle, medial tibial plateau, and lateral tibial plateau was evaluated according to the

classification method for articular cartilage injury of Andresen *et al.*¹⁵. Bone erosion was defined by the following criteria: hyperintensity on STIR sequences and hypointensity on T1WI; direct contact with cortical bone; well-defined margins; and apparent destruction of the adjacent cortical bone. Bone marrow edema was defined by hyperintensity on STIR sequences, with less clearly defined margins and intact trabecular structures of the bone⁹. The degree of destruction of the medial and lateral menisci was classified based on the revised methods of Stoller *et al.*¹⁶, as follows: first degree destruction, patchy high SI inside the menisci on PDWI; second degree destruction, linear high SI in the menisci on PDWI; third degree destruction, large areas of high SI in the menisci on PDWI, extending to the surface of the meniscus; and fourth degree of destruction, thinning, atrophy, and heterogeneous high SI in the menisci on PDWI. Synovitis was identified as a thickening of the synovium, with hypointensity to isointensity on T1WI and hyperintensity on STIR sequences¹². The stage of knee joints in RA patients was assessed based on the evaluation criteria of Larsen *et al.*¹⁷, and we modified the criteria to make it more suitable to MR classification. Stage 0: normal conditions; Stage 1: slight articular cartilage thinning of the medial and lateral tibiofemoral joints without bone erosion; Stage 2: moderate articular cartilage thinning of the medial and lateral tibiofemoral joints with bone erosion; Stage 3: severe articular cartilage thinning of the medial and lateral tibiofemoral joints with bone erosion; and Stage 4: disappearance of the articular cartilage of the medial and lateral tibiofemoral joints with bone erosion. All images were evaluated by two radiologists (X.H. M. and Z.W.), who have 7 and 30 years of experience, respectively, in evaluating musculoskeletal MRI. The degree of destruction, the number of structures involved, and the classification of the knee joints in RA patients were confirmed by consensus.

Histological Examinations

After TKA, knee specimens were acquired, including the distal femur and proximal tibia. Specimens were labeled with careful recording of the site and the orientation of the bone for later comparison between MRI and histological slides. All the samples were fixed in 10% formalin. The bone and cartilage samples were subsequently demineralized at room temperature in a 10% sulfuric acid solution and then embedded in paraffin. Consecutive sections were made, 4 microns apart. Sections were mounted on glass slides and stained with hematoxylin and eosin. All the sections were analyzed semiquantitatively, using a histomorphometric technique under microscope (CH-2, Olympus, Japan). When the pathologist was uncertain about the origin of cells, immunohistochemical examinations were performed for confirmation. Sections used for regular histological examinations were also used for immunohistochemical examinations, as needed. The paraffin-embedded sections were dewaxed, heated in a microwave oven in citrate buffer (0.1%, pH 6.0) for antigen retrieval, and then incubated for 16 min at 90 °C. Monoclonal antibodies against the

following antigens were used: CD68 (working solution, clonePG-M1, GENENTECH, Shanghai, China) expressed in histocytes, CD38 (working solution, clone VS38C, GENENTECH) expressed in plasmocytes, CD20 (working solution, clone L26, GENENTECH) expressed in B lymphocytes, CD45RO (working solution, clone UCHL1, GENENTECH) expressed in T lymphocytes, and CD34 (working solution, clone QBEnd-10, GENENTECH) expressed in vascular endothelial cells. Sections were subsequently incubated for 30 min with a biotinylated antimouse secondary antibody. The color reaction was developed using a DAB (GTVision III, GENENTECH) as chromogen. All incubations were carried out at room temperature, and sections were washed with phosphate buffered saline between each step.

The degree of severity of histological findings was classified semiquantitatively, using a 3-point scale: “0”, histological findings are within normal limits; “1”, abnormal histological findings in $\leq 1/3$ of the area of the slice; “2”, abnormal histological findings in $1/3$ to $2/3$ of the area of the slice; and “3”, abnormal histological findings in $>2/3$ of the area in a slice. The average degree of histological findings was then calculated. All histological examinations were performed by one pathologist (J.X., with >30 years of experience in musculoskeletal pathology), who was blinded to the MRI results.

Statistical Analysis

The degree of destruction in articular cartilage on the medial and lateral femoral condyles, medial and lateral tibial plateaus, and medial and lateral menisci, identified on MRI, was summarized and averaged across all specimens. Analysis of variance (ANOVA), with a least squared difference (LSD) post-hoc test, was used to evaluate the difference in the degree of cartilage destruction between the medial and lateral femoral condyles and the medial and lateral tibial plateaus. A Mann–Whitney *U*-test was used to compare the difference in degree of destruction between the medial and lateral menisci. The occurrence of bone erosion, bone marrow edema, and synovitis was summed across all specimens. Histological findings in the articular cartilage, areas of bone erosion and of bone marrow edema, the menisci, and the synovitis were classified semiquantitatively, and the mean $\pm$ SD extent of destruction for each tissue was calculated across all specimens. A Mann–Whitney *U*-test was used to compare the histological differences between the areas of bone erosion and bone marrow edema. A *P*-value <0.05 was considered statistically significant for all analyses.

Results

Description of the Study Group

Over the 3-year period of the study, 22 consecutive patients, who met our inclusion/exclusion criteria, were enrolled in the study. Among these, 4 were scheduled for bilateral TKA. Accordingly, 26 knee joints were included in the study (12 left and 14 right knees; from 4 men and 18 women; age

range, 25–58 years, mean, 52.81 ± 9.58 years). Of the 26 knee joints, 1 joint was at stage 2, 21 at stage 3, and 4 at stage 4.

Correlation of MRI to Histological Findings for Articular Cartilage

For most patients, the extent of articular destruction was classified as grade 4 for the medial and lateral femoral condyles and the medial and lateral tibial plateaus, with an average destruction grade of 3.6 ($F = 5.455$, $P = 0.002$); the destruction grade of the medial femoral condyles was 3.69, of the lateral femoral condyles was 3.85, and of the medial and lateral tibial plateaus were 3.23 and 3.62, respectively. Therefore, the average degree of destruction of knee joint cartilage was severe on MRI overall. Of note, the degree of destruction was the least severe on the lateral femoral condyle. The majority of knee joints were stage 3 or 4 due to severe thinning or disappearance of the articular cartilage in medial and lateral tibiofemoral joints, suggesting that the function of the articular cartilage in these patients was lost and that TKA was necessary. Histological findings of articular cartilage destruction are summarized in Table 1 and include the presence of synovial lining cells on the surface of the cartilage, fibrosis of the superficial layer, granulation tissue formation, thinning and destruction of the cartilage, fissure and necrosis, cartilage hyperplasia, bone exposure, and vascular invasion. Fibrosis, thinning, and destruction of the cartilage and hyperplasia were the most severe histological findings, and were indicative of a process of cartilage destruction and repair. The synovium was found on the cartilage, which may have led to the destruction of cartilage.

Correlation of MRI to Histological Findings for Bone Marrow Edema and Bone Erosion

On MRI, there were 36 locations of bone marrow edema, which were distant from the bare areas, while 68 locations of bone erosion were located in the bare areas (Fig. 1). The histological findings in these areas consisted of bone necrosis, microfracture and callus formation of the bone, vascular hyperplasia and dilation, bone absorption by osteoclasts, osteoporosis, fibrosis, lymphocyte infiltration, plasmacyte infiltration, and a mosaic structure of the bone in the area (Table 2). Fibrosis, mosaic structure, and lymphocyte

Fig. 1 Representative cartilage and bone lesions in the right knee of a 62-year-old woman with rheumatoid arthritis. The sagittal short time of inversion recovery (STIR) proton density weighted imaging (PDWI) sequence (A) and the T1WI spoiled gradient echo (SPGR) sequence (B) revealed a thinning and destruction (arrow head) of the articular cartilage of the lateral tibiofemoral joint, with synovial infiltration and erosion (star) of the subchondral bone. The coronal PDWI STIR (C) sequence revealed thinning and atrophy (arrow head) of the medial and lateral menisci, and bone marrow edema of the subchondral bone of the lateral tibiofemoral joint (star). The traverse fat suppression T2WI (D) revealed diffuse synovial thickening in the knee joint (arrow).

infiltration were the most severe histological findings. The comparison of histological findings between bone erosion and bone marrow edema is summarized in Table 3. Of note,

TABLE 1 Histological findings and classification in articular cartilage of knee joints in patients with RA (mean $\pm$ SD)

Area	Synovial lining cells covering	Fibrosis of the superficial layer	Granulation tissue formation	Thinning and destruction	Fissure and necrosis	Hyperplasia	Bone exposure	Vascular invasion
LTP	0.85 ± 0.90	1.69 ± 1.10	1.38 ± 0.96	1.38 ± 0.77	1.08 ± 0.95	1.23 ± 1.09	0.85 ± 0.99	0.54 ± 0.97
LFC	0.62 ± 0.87	1.54 ± 1.05	1.00 ± 1.00	1.38 ± 1.04	1.08 ± 1.04	1.31 ± 1.31	0.69 ± 0.95	1.00 ± 1.00
MTP	0.69 ± 0.95	1.54 ± 1.12	1.23 ± 1.01	2.15 ± 0.69	1.00 ± 1.00	1.85 ± 0.90	1.00 ± 0.82	0.31 ± 0.48
MFC	0.85 ± 1.00	1.92 ± 0.76	1.46 ± 0.88	1.31 ± 1.03	0.69 ± 0.63	1.15 ± 0.99	0.92 ± 1.19	1.50 ± 1.31
Average	0.75 ± 0.93	1.67 ± 1.00	1.27 ± 0.95	1.56 ± 0.94	0.96 ± 0.91	1.38 ± 1.09	0.87 ± 0.97	0.81 ± 1.05

LFC, lateral femoral condyle; LTP, lateral tibial plateau; MFC, medial femoral condyle; MTP, medial tibial plateau; RA, rheumatoid arthritis

TABLE 2 Histological findings and classification in subchondral bones of knees joints in patients with RA (mean $\pm$ SD)

Area	Necrosis	Microfracture and callus formation	Vascular hyperplasia and dilation	Bone absorption by osteoclasts	Osteoporosis	Fibrosis	Lymphocytes infiltration	Plasmacytes infiltration	Mosaic structure
LTP	0.00 $\pm$ 0.00	1.00 $\pm$ 1.00	0.77 $\pm$ 0.73	0.62 $\pm$ 0.77	0.92 $\pm$ 0.76	0.92 $\pm$ 0.76	1.54 $\pm$ 1.05	1.15 $\pm$ 1.07	1.15 $\pm$ 0.90
LFC	0.08 $\pm$ 0.28	0.62 $\pm$ 0.87	0.54 $\pm$ 0.66	0.54 $\pm$ 0.66	0.77 $\pm$ 0.44	1.15 $\pm$ 1.07	0.92 $\pm$ 1.04	0.62 $\pm$ 0.77	1.00 $\pm$ 1.30
MTP	0.31 $\pm$ 0.48	1.08 $\pm$ 0.95	0.69 $\pm$ 0.63	1.08 $\pm$ 0.76	0.69 $\pm$ 0.86	1.46 $\pm$ 1.13	1.23 $\pm$ 0.83	1.00 $\pm$ 0.71	1.77 $\pm$ 0.93
MFC	0.31 $\pm$ 0.63	0.85 $\pm$ 1.21	1.08 $\pm$ 0.95	1.00 $\pm$ 1.00	1.15 $\pm$ 1.07	1.54 $\pm$ 0.97	1.15 $\pm$ 0.90	1.23 $\pm$ 0.73	1.00 $\pm$ 0.91
Average	0.17 $\pm$ 0.43	0.88 $\pm$ 1.00	0.77 $\pm$ 0.76	0.81 $\pm$ 0.82	0.88 $\pm$ 0.81	1.27 $\pm$ 1.00	1.21 $\pm$ 0.96	1.00 $\pm$ 0.84	1.23 $\pm$ 1.04

LFC, lateral femoral condyle; LTP, lateral tibial plateau; MFC, medial femoral condyle; MTP, medial tibial plateau; RA, rheumatoid arthritis

areas of bone marrow edema and bone erosion both included inflammatory infiltrates and showed degenerative changes, and the inflammatory infiltrates were more obvious in areas of bone erosion, although this difference was not significant, which may be due to the bone erosion needing more inflammatory cells. The degenerative changes in the areas of bone marrow edema and bone erosion were a secondary reparative process to the bone destruction.

Correlation of MRI to Histological Findings for the Menisci

The degree of meniscus destruction was classified as grade 4 in the majority of patients, for both the medial and lateral meniscus, with an average degree of meniscal destruction over all specimens of 3.85; the destruction grade of the medial meniscus was 4 and of the lateral meniscus was 3.69. Atrophy and severe destructions of the menisci are, therefore, characteristic features of RA on MRI. The degree of destruction was more severe for the medial meniscus than for the lateral meniscus ($Z = -2.062$, $P = 0.039$). Among all specimens, 10 menisci were available (19.2%, 10/52), with complete destruction of the menisci in the other specimens. The histological findings of the menisci in RA included (the degree of severity of histological findings is marked in parentheses): synovial cells on the meniscal surface (1.00 $\pm$ 0.00), fibrosis (1.80 $\pm$ 0.84), fibrinoid necrosis (1.40 $\pm$ 0.89), vascular hyperplasia (1.20 $\pm$ 0.84), lymphocyte infiltration (1.00 $\pm$ 0.71), plasmacyte infiltration (1.00 $\pm$ 0.00), and

engulfing and encapsulating calcified debris (1.60 $\pm$ 0.55). Fibrosis, engulfing and encapsulating calcified debris, and fibrinoid necrosis were the most severe histological findings. In cases in which the menisci had been completely destroyed, synovium was identified on the surface of the menisci, which may be the main cause of meniscal destruction.

Correlation of MRI to Histological Findings for the Synovium

On MRI, a synovitis was identified in all patients, including synovial hyperplasia, showing as a high SI on PDWI and T2WI. The histological findings of the synovitis in RA included (the degree of severity of histological findings is marked in parentheses): hyperplasia of intima cells (2.27 $\pm$ 0.90), multinucleated giant cell infiltration (0.91 $\pm$ 1.04), fibrinoid necrosis (1.82 $\pm$ 0.69), lymphocyte infiltration (2.18 $\pm$ 0.60), plasmacyte infiltration (2.18 $\pm$ 0.75), vascular hyperplasia and dilation (2.18 $\pm$ 0.60), hemorrhage and hemosiderin deposition (1.55 $\pm$ 0.69), fat metaplasia (0.73 $\pm$ 0.71), interstitial fibrosis (2.09 $\pm$ 0.70), and engulfing and encapsulating bony and cartilage debris (1.55 $\pm$ 0.93). Hyperplasia of intima cells, lymphocyte and plasma cell infiltration, and vascular hyperplasia and dilation were the most severe histological findings of synovitis. The pannus was formed of synovium infiltrated by inflammatory cells and filled with blood vessels. The pannus can infiltrate and destroy neighboring structures.

TABLE 3 Comparison of histological findings between the areas in bone marrow edema and in the bone erosion (mean $\pm$ SD)

Types	Necrosis	Microfracture and callus formation	Vascular hyperplasia and dilation	Bone absorption by osteoclasts	Osteoporosis	Fibrosis	Lymphocytes infiltration	Plasmacytes infiltration	Mosaic structure
Bone marrow edema	0.33 $\pm$ 0.59	0.89 $\pm$ 1.02	0.89 $\pm$ 0.90	0.67 $\pm$ 0.77	0.78 $\pm$ 0.55	1.11 $\pm$ 1.08	1.00 $\pm$ 0.84	0.72 $\pm$ 0.67	1.17 $\pm$ 1.10
Bone erosion	0.12 $\pm$ 0.33	0.88 $\pm$ 1.01	0.71 $\pm$ 0.68	0.88 $\pm$ 0.84	1.06 $\pm$ 0.92	1.35 $\pm$ 0.95	1.32 $\pm$ 1.01	1.15 $\pm$ 0.89	1.26 $\pm$ 1.02
Z-scores	-1.494	0.000	-0.565	-0.935	-1.043	-0.862	-1.112	-1.658	-0.391
P values	0.135	1.000	0.572	0.350	0.297	0.389	0.266	0.097	0.696

Discussion

Rheumatoid arthritis typically affects the joints of the hands and feet, with the knee joint also being commonly affected. Characteristic MRI manifestations of knee joint RA included severe articular cartilage and the menisci destruction. Bone erosion and bone marrow edema were both identified in RA patients; both lesions had the same pathological features. However, synovitis was identified in all patients, with histological findings of fibrosis and inflammatory cell infiltration.

MRI and Histological Correlations of Cartilage in Rheumatoid Arthritis Patients

Our findings of irregular and thinning cartilage, with some areas of exposed subchondral bone on MRI concurred with findings by Chaplin⁵, who reported cartilage damage of the femoral condyles, with or without evidence of patellar or tibial cartilage damage, in 45 of the 50 cases of knee OA in their study. In their observational study, Chaplin reported that the cartilage destruction extended from the lateral margins of the femoral condyles to the intercondylar notch. The origin of the cartilage destruction in RA has been, and continues to be, debated. Fujimori *et al.* proposed that bone marrow edema was associated with cartilage loss in RA¹⁸. Herz *et al.* reported that both synovitis and bone marrow edema were associated with cartilage damage in the metacarpophalangeal joints of patients with RA¹⁹. Other researchers have suggested that the matrix metalloproteinase and matrix-degrading enzymes released by the inflammatory cells in the synovium are responsible for cleaving cartilage components, with local chondrocytes subsequently synthesizing and locally releasing cytokines, which accelerates the switch from an anabolic to a catabolic state in the cartilage^{20,21}. Walsh *et al.* demonstrated that new blood vessels within the articular cartilage originate from the bone marrow of the subchondral bone, with the resulting osteochondral angiogenesis being associated with fibrovascular marrow replacement²². In our study, we identified synovial cells covering the surface of cartilage. It is possible that inflammatory cells and chemokines in the synovium may infiltrate and destroy the cartilage. We also identified vascular invasion of the cartilage, which may originate from either the synovium or the subchondral bone. These findings can explain the thinning of cartilage and exposure of the subchondral bone on MRI. Moreover, the findings of cartilage hyperplasia and formation of granulation tissue indicates an attempt to repair the damage to the cartilage.

MRI and Histological Correlations of Bone Marrow Edema and Bone Erosion in Rheumatoid Arthritis Patients

Hetland *et al.* reported that the bone marrow edema score was the strongest independent predictor of radiographic progression of cartilage destruction in a randomized controlled trial²³. McQueen and Ostendorf similarly reported that a high MRI grade of bone marrow edema was commonly observable

within the field of intended surgery, and was associated with pain²⁴. Therefore, MRI-based detection of bone marrow edema in patients with RA is of clinical importance. Among the 26 specimens in our study group, we identified 36 locations of bone marrow edema and 68 of bone erosion, with histological findings being comparable for both sites. Due to the infiltration of inflammatory cells, which increases the water content, bone marrow edema shows as a high SI on STIR T2WI and PDWI sequences. Dalbeth *et al.* reported the density of osteoclasts, macrophages, plasma cells, and B cells to be higher in tissue samples with bone marrow edema compared to samples without edema²⁵. Jimenez-Boj *et al.* reported that areas of erosion in the cortical bone had been fenestrated by synovial inflammatory tissue, with lymphocytes and blood vessels detected at the interface between synovial tissue and the bone marrow⁹. This implies a role of inflammatory infiltrates in the development of bone marrow edema, although the infiltration tended not to be severe and was localized to more central regions of the bone marrow. Bugatti *et al.* proposed that the marked increase in bone resorption is likely to be mediated by osteoclasts at the pannus-bone interface and in the marrow of subchondral bone, which, combined with impairment in osteoblast differentiation and function, results in a net loss of bone¹⁰. Several pro-inflammatory cytokines have been identified in the pannus, including tumor necrosis factor (TNF)- α , interleukin (IL)-6, IL-1, and IL-17, which further stimulate osteoclasts differentiation and activation. In our histological examination, we identified infiltration of inflammatory cells, osteoclasts, osteoporosis, and vascular hyperplasia in areas of bone marrow edema and bone erosion. The findings from these two sites had no significant difference, which implies that the destruction mechanisms are the same. We also observed bone necrosis, microfracture, and callus formation in these areas, which were consistent with previously reported findings in knee joint osteoarthritis^{26,27}. As the majority of patients recruited in our study were middle-aged, findings of features of knee osteoarthritis are not unreasonable. The destructive features of RA on joint structures could accelerate the development of knee osteoarthritis at an earlier age.

MRI and Histological Correlations of Menisci in Rheumatoid Arthritis Patients

Few studies have reported on the destruction of the knee menisci in RA. We identified a severe destruction of menisci with RA, with manifestations of atrophy, thinning, and heterogeneous SI on MRI. Moreover, the extent of destruction was more severe for the medial meniscus than for the lateral meniscus. In most of our cases (48/52, 92.3%), the menisci had been completely destroyed on MRI, a finding that is in agreement with Kimura and Vainio⁶, who found that the menisci underwent a more rapid process of degeneration than cartilage, with an incomplete or complete absence of the menisci identified in 39 of their 47 cases. Kimura and Vainio also found greater destruction of the medial meniscus than of the lateral meniscus. In our study, the synovial cells

were found on the surface of the menisci, which would release mediators and cytokines and further degrade the menisci. This is supported by our findings of fibrosis and fibrinoid necrosis inside the meniscus, suggestive of a complete destruction of the meniscus, which would explain the observed atrophy of the meniscus and the heterogeneous SI for this structure.

MRI and Histological Correlations of Synovia in Rheumatoid Arthritis Patients

The synovium is the primary target of changed immunomodulatory pathways in RA^{28,29}. Normal synovial tissue is comprised of one to three layers of specialized columnar fibroblast-like synoviocytes, which are interspersed with macrophages. In patients with RA, macroscopically, synovial tissue appears hyperplastic and hypervascular, with hyperplasia of the intimal layer and accumulation of inflammatory cells and chemokines, including T and B lymphocytes, plasma cells, macrophages, neutrophils, mast cells, natural killer cells, dendritic cells, immune complexes, citrullinated fibrinogen, and complement component C3, identified in the synovial sublining layer on microscopic analysis^{3,28,30}. The thickened synovium is also characterized by increased vascularity, which is a result of angiogenesis. The angiogenesis is in an immature state, which allows increased leukocyte migration, transforming the synovial tissue into an invading pannus that can cause cartilage and bone destruction^{28,31}. Our findings with regard to the changes in the synovial lining are consistent with those of previous studies. In specimens in our study, the synovium was thickened and had a low SI on the T1WI MRI sequence and high SI on the T2WI and PDWI sequences, reflecting the hyperplasia of the intima cells, in combination with inflammatory cell infiltration and angiogenesis. Synovial infiltration is likely to be the primary

mechanism leading to the destruction of the articular cartilage and menisci, and the areas of bone erosion.

Limitations

We have several limitations in this study which need to be considered in the interpretation of results. First, the sample size was relatively small, reflecting the overall low number of patients with knee RA who undergo TKA. A more suitable model for MRI and histological studies of knee RA is needed. Second, we did not recruit patients with knee joint osteoarthritis to provide a comparator group. However, we demonstrated that the MRI and histological manifestations of osteoarthritis in the knee are well-described and can be reliably differentiated from those of RA. Third, patients enrolled in our study were in the late stage of RA and, therefore, our findings do not provide insight into the evolution of knee joint destruction in RA. Animal models would be suitable to clarify the evolution of RA, and to correlate MRI and histological examinations.

Conclusion

The severe destruction of the articular cartilage and the menisci are characteristic features of knee joint RA. Infiltration of the synovium is likely to be the primary cause of this destruction by allowing infiltration of inflammatory cells. Bone marrow edema and bone erosion have the same pathological features. However, the pathogenesis of bone marrow edema remains to be elucidated.

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