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Bone marrow lesions, subchondral bone cysts and subchondral bone attrition are associated with histological synovitis in patients with end-stage knee osteoarthritis: a cross-sectional study

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SUMMARY

Objective: The aim of this study was to examine the osteoarthritis (OA)-related structural changes associated with histological synovitis in end-stage knee OA patients.
Methods: Forty end-stage knee OA patients (female: 88%, mean age: 71.8 y) were enrolled. All participants underwent 3.0-T MRI. The structural changes, such as cartilage morphology, subchondral bone marrow lesion (BML), subchondral bone cyst (SBC), subchondral bone attrition (SBA), osteophytes, meniscal lesion and synovitis, were scored using the whole-organ MRI scoring (WORMS) method. Synovial samples were obtained from five regions of interest (ROIs) of the knee joint during total joint replacement surgery. The associations between the histological synovitis score (HSS) and WORMS or the synovial expression levels of cyclooxygenase (COX)-2, interleukin (IL)-1β, IL-6 and transforming growth factor (TGF)−β were examined using Spearman's correlation coefficient.
Results: Among the seven OA-related structural changes, the BML, SBC, SBA and synovitis were significantly associated with the HSS ($r = 0.33$, 0.35, 0.48 and 0.36, respectively), while other morphological changes were not. Although synovial COX-2, IL-1β or IL-6 expression levels were not associated with the HSS, the synovial TGF-β expression levels were associated with the HSS.
Conclusion: The presence of BML, SBC and SBA was associated with histological synovitis in end-stage knee OA patients.

Introduction

There are no disease-modifying osteoarthritis (OA) drugs available for treating knee OA at present, and symptom-modifying therapy is the only available treatment for knee OA[1–3]. Despite the importance of the symptoms of the disease, much remains unknown regarding the nature, causes and natural history of OA symptoms.

Pain is the most prominent and disabling symptom of knee OA[4,5]. Because OA-associated joint damage may be associated with clinical problems, the joint damage associated with the pain and the pathogenesis of pain must be investigated[6]. However, the

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severity of joint disease is only weakly related to the clinical findings according to classic radiographic techniques[2].

Although OA was considered to be a non-inflammatory condition, the role of synovitis in OA has attracted particular attention[7,8]. It was recently reported that synovial inflammation could play an important role in the pathophysiology of OA[9–13]. Synovitis in OA may be a secondary phenomenon related to the cartilage alterations induced by the release of degenerative compounds from the extracellular matrix of articular cartilage in response to the presence of microcrystals in the synovial fluid and in the synovium[11,14]. However, most of the previous studies focused on synovitis in OA were conducted on patients with early-to advanced-stage knee OA.

We previously revealed that the symptoms of patients with end-stage knee OA who required total knee arthroplasty (TKA) showed a significant correlation with the severity of synovitis in the affected knee joint[15]. On the other hand, no joint structural changes evaluated by classic radiography were associated with the pain and symptoms of these patients. In addition, it has remained unclear whether synovitis is also related to cartilage alterations or other features in patients with end-stage knee OA, where the articular cartilage has been nearly lost. We also previously reported that the cytokine profiles of the synovium in patients with end-stage knee OA were different from those in patients with early-stage knee OA[13].

The interest in developing other treatments for OA has stimulated the search for more sensitive indicators of OA for use in conjunction with the traditional radiographic outcomes. Magnetic resonance imaging (MRI) measurements, in addition to biomarkers, have sufficient sensitivity to detect OA-related structural changes[16,17]. MRI is currently being optimized for OA imaging and is more sensitive than radiographic techniques to detect bone and soft tissue changes, which are features of OA[18]. MRI can also provide a wealth of information on the pathology of knee OA, its natural history and the structure–pain relationships, which is not obtainable using radiography[19]. The semi-quantitative whole-organ MRI scoring (WORMS) method offers an initial instrument for performing multi-feature assessments of the knee using conventional MRI[20].

The aim of our present study was to investigate whether the MRI-detected structural changes of the knee joint were associated with histological synovitis in patients with end-stage knee OA who underwent TKA.

Patient and methods

Subjects

Forty patients who fulfilled the American College of Rheumatology criteria for knee OA[21] and who received TKA were enrolled in this study. This study was approved by the institutional ethical review committee of our university. Written informed consent was obtained from all participating patients.

Clinical manifestations

The clinical manifestations were evaluated using the Japanese Knee Osteoarthritis Measure (JKOM) score[22] and the pain was evaluated using the visual analog scale (VAS, 0–100). The JKOM is a patient-based, self-answered evaluation score that includes four subcategories: pain and stiffness, activities of daily living, social activities, and general health conditions with 100 points as the maximum score. The JKOM score is higher in patients with more pain and physical disabilities, and this evaluation modality is considered to have sufficient reliability and validity for studies of the clinical outcomes of Japanese people with knee OA.

Radiographic evaluation of knee OA

The standing, extended and anteroposterior and lateral view radiographs and the posteroanterior weight-bearing radiograph made with the knee in 45° of flexion (Rosenberg radiograph) were taken at the admission for the operation[23,24]. In addition to the evaluation of the Kellgren and Lawrence (K/L) grade[25] and the femorotibial angle (FTA), the joint space width (JSW) was determined at the center point of the medial femorotibial compartment on a radiograph. All radiographs were quantified independently by two readers (AY, LL and RS) who were blinded to the baseline characteristics of the patients.

MRI-based evaluation of knee OA

All patients showed a K/L grade 4[25] and were also examined with the MAGNETOM Verio MR 3.0-T MRI system (Siemens Medical Solutions, Erlangen, Germany) according to the previously reported method[17]. The knee was scored using the WORMS method[20]. Specifically, three regions (anterior, central and posterior) of the medial and lateral femoral condyles and tibial plateaus, and two regions (medial and lateral) of the patella were each scored separately for the cartilage morphology, bone marrow lesion (BML), subchondral bone cyst (SBC), subchondral bone attrition (SBA) and osteophytes. Each region of a compartment surface received its own score, following the method reported previously[17,20]. At each region, the cartilage morphology was given a score of 0–6. The BML and SBC were given a score of 0–3. The SBA was scored 0–3. Osteophytes were scored 0–7. The anterior horn, posterior horn, and body of the medial and lateral meniscus were each graded 0–4. A cumulative grade for each meniscus was also determined using a score of 0–6. No intravenous contrast was injected in this study, which thus precluded us from differentiating synovial thickening and joint effusion. Thickening and effusion were therefore graded collectively as per the WORMS protocol from with a score of 0–3 for synovitis[20].

The intra-observer reproducibility (AY) of the MRI evaluation of OA was measured at separate times for twenty patients [inter-class correlation coefficient (ICC): 0.81 (95% CI: 0.79–0.84)]. AY and RS independently conducted the MRI evaluation. To confirm their accuracy for the MRI evaluation, the musculoskeletal radiologist (KOK) also independently conducted the MRI evaluation. The inter-observer reproducibility was measured between these three observers (AY, RS and KOK) who conducted 20 examinations [ICC between AY and RS: 0.71 (95% CI: 0.68–0.75), ICC between AY and KOK: 0.72 (95% CI: 0.68–0.75) and ICC between RS and KOK: 0.69 (95% CI: 0.61–0.75)].

Histological examination

Sample preparation

Synovial tissue samples were obtained from the patients at the time of the operation from five regions of interest (ROIs)[26]. They included three in the suprapatellar recess [lateral recess (ROI 1), medial recess (ROI 2)], and just above the trochlear groove (ROI 5), and one each in the lateral and medial distal femoral gutters (ROIs 3 and 4, respectively). The synovial tissue samples were fixed in 10% neutral buffered formalin, and subsequently processed by standard histological techniques, followed by mounting in paraffin blocks for sectioning. The 5-μm paraffin sections were stained with hematoxylin and eosin for a microscopic analysis[13,15]. The staining procedures were performed consecutively at one time for all the sections. Ten sections were randomly selected from 30 sections per sample from one ROI. For one section, five examination fields (EFs) which included synovial articular surfaces were randomly selected

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