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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Abstract

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-Tesla 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 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
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 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-Tesla 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 using a special eye-piece with a 10×10-grid frame. Six inflammatory parameters described below were studied in each of the EFs under 200x magnification [26].

**The histological parameters**

The six histological parameters were: (1) the thickness of the synovial lining layer, (2) subsynovial infiltration by lymphocytes and plasma cells, (3) surface fibrin deposition, (4) blood vessel vasodilation and blood vessel proliferation, (5) fibrosis, and (6) perivascular edema. The parameters were graded as follows: 0, none; 1, mild; 2, moderate; and 3, severe. Grade 0 corresponded to normal synovial tissue, and grade 3 corresponded to the most severe pattern observed in the OA samples.

The histological examiner (AY) was blinded to all data. The mean of each of the parameters for five EFs was used to represent the section. The procedures were undertaken for 10 sections for each parameter, and the mean of each of these 10 sections was used to represent each ROI. The procedures were repeated for the five ROI specimens. The mean of
each parameter from the five ROIs was considered to represent the histological parameters of
the patients. The average of the six histological parameters was calculated to give a mean total
histological synovitis score (HSS) for the patient.

**Immunohistochemical staining**

Similar to chondrocytes, the synovial cells of OA patients produce inflammatory cytokines,
such as interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α, which in turn decrease
anabolic collagen synthesis and increase catabolic mediators, such as matrix
metalloproteinase (MMP)-1 and MMP-13, via their subsequent intracellular signaling through
nuclear factor kappa B (NF-κB) and cyclooxygenase (COX)-2 [27]. Therefore, among these
molecules, IL-1β, COX-2 and IL-6 expression levels in the synovium were examined in the
present study. We also examined the synovial expression levels of transforming growth factor
(TGF)-β, which is also known to be expressed in the synovium in knee OA [7]. The 5-µm
paraffin sections (the same samples used for HE staining) were stained for TGF-β (TB21,
AbD Serotec, Kidlington; 1:5,000 dilution) [28], COX-2 (33/COX-2, BD Biosciences,
Franklin Lakes, USA; 1:50 dilution) [10], IL-1β (MAB601; R&D Systems, Wiesbaden,
Germany; 1:20 dilution) [28] and IL-6 (MAB2061; R&D Systems, Wiesbaden, Germany;
1:300 dilution) [29]. A semi-quantitative analysis of the stained sections was conducted, as
previously reported [13, 30]. The number of positively-stained cells was estimated in ten
high-powered fields (400x) chosen at random. In each high-powered field, three histological findings of the synovium, including the vasculature, synovial sublining layer and the synovial lining layer, were scored separately according to the scoring system. Each section was scored on a scale from 0-3 to reflect the degree of specific staining as follows: 0 represented 0-5% positive staining, 1 represented 6-29%, 2 indicated 30-59% and 3 indicated $\geq 60\%$ staining. The cumulative staining scores were calculated by summing the mean score of these four parameters for each case.

The intra-observer reproducibility (AY) of the histological scores was measured at separate times for ten sections [ICC: 0.97 (95% CI: 0.94 - 0.98)]. The inter-observer reproducibility was measured by two observers [AY and LL for HE, AY and LN for immunohistochemistry] who conducted 10 examinations ([ICC: 0.94 (95% CI: 0.89 - 0.97)] and [ICC: 0.93 (95% CI: 0.86 - 0.96)], respectively).

**Statistical analysis**

Spearman’s correlation coefficient was used to investigate the correlation of either the MRI-detected OA-related joint structural changes or the inflammatory cytokines and growth factor with histological synovitis in the patients. A $p$-value < 0.05 was considered to be statistically significant. The SPSS 19.0 software program (SPSS Institute, Chicago, IL, USA) was used for the statistical analysis.
Results

Patient characteristics

The characteristics of the patients in the present study are shown in Table 1. All patients had medial type knee OA with a K/L grade of 4 for the radiographic OA severity, and most of the patients were female (88%). The HSSs of the patients were significantly associated with the symptoms evaluated by the JKOM score ($r = 0.345, p = 0.03$), consistent with the findings of a previous study [15].

The MRI-detected joint structural changes associated with synovitis in the patients

Among the OA joint changes evaluated by the WORMS analysis, the BML score, SBC score, SBA score and synovitis scores were associated with the HSSs of the patients (Figure 1), while other joint structural changes, such as the cartilage morphology score, osteophyte score and meniscal pathology scores, were not (Table 2).

Associations between synovitis and the synovial expression levels of inflammatory mediators and growth factors in the patients

No associations were observed between the synovial IL-1β expression levels and the HSSs of the patients (Table 3). Similarly, neither synovial COX-2 expression levels nor synovial IL-6 expression levels were associated with the HSSs of the patients (Table 3). Although the
TGF-β expression in the synovial lining and sublining layers were not associated with the HSSs of the patients, the TGF-β expression in the vasculature of the synovium were associated with the HSSs of the patients (Table 3).
**Discussion**

We previously reported that synovitis in the knee joint was associated with the symptoms in patients with end-stage knee OA who received TKA [15]. However, the OA-related structural changes associated with synovitis have remained unclear. In the present study, we examined the OA-related structural changes using MRI to determine which changes were associated with histological synovitis in patients with end-stage knee OA who underwent TKA. We found that the presence of subchondral pathologies, such as BML, SBC and SBA, in addition to MRI-detected synovitis, was significantly associated with the presence of histological synovitis in patients with end-stage knee OA. The inflammatory mediators known to be involved in the pathophysiology of OA [7], such as COX-2, IL-1β and IL-6, were not associated with the histological synovitis in patients with end-stage knee OA. On the other hand, the synovial expression of TGF-β, which is a growth factor known to be involved in the pathophysiology of OA [31], was associated with histological synovitis in patients with end-stage knee OA. Our study demonstrated the associations between BML, SBC and SBA, synovial TGF-β expression and histological synovitis in patients with end-stage knee OA, which were not previously well established in the literature.

Because synovitis in knee OA occurs locally in areas of cartilage loss [11], the medial type of knee OA shows medial local synovitis, which is associated with cartilage degradation. In
the medial type of knee OA, the number of anti-type II collagen-positive fragments, which is one of the causes of synovitis in the medial compartment of the knee, was higher than that found in the lateral compartment [32]. In the present study, the presence of subchondral pathologies, such as BML, SBC and SBA, was associated with synovitis. These data suggest that synovitis is present not only in early-stage but also end-stage knee OA and is possibly induced by not only articular cartilage destruction but also, at least in part, due to the subchondral pathologies.

We previously reported that the factors associated with the pain severity in patients with knee OA varied with the radiographic disease severity [33]. The serum levels of IL-6, which is related to synovitis, were mainly associated with the pain severity in early-stage knee OA, while the anatomical axis angle, which represents the detrimental mechanical loading across the joint, was mainly associated with that in advanced- to end-stage knee OA.

As the expression of COX-2, IL-1β and IL-6 in synovial tissues is thought to be activated by degenerated articular cartilage, the expression of these inflammatory mediators would be expected to be enhanced in the synovial tissues dependent on the severity of the disease. However, the expression levels of these cytokines in patients with end-stage knee OA were decreased in comparison to those in patients with early- to advanced-stage knee OA in previous studies [12, 13]. In contrast, the expression levels of TGF-β in the synovium were
increased depending on the severity of the disease in patients with the medial type of knee OA [13].

BMLs are suggested to be one of the pathological features related to detrimental mechanical loading across the joint [18, 34-36]. Prevalent and incident SBA is strongly associated with BMLs in the same subregion [37]. BML has also been revealed to be associated with the progression of OA [18, 34, 36, 38]. The enlargement of BML was associated with the progression of the disease [34]. The malalignment of the lower limbs was associated with both the incident risk and the enlargement of BML in the more loaded compartments of the knee joint [35]. As all patients in the present study showed the medial type of knee OA, BMLs were observed in the medial compartments of the knee joint in all patients who showed varus lower-limb alignment (FTA: 184.9° on average). Although COX-2, IL-1β and IL-6 may be produced by and/or related to the cartilage destruction in knee OA, limited articular cartilage remained and the subchondral bone showed eburnation, especially in the medial compartment of the knee joint of patients with end-stage medial type of knee OA in the present study. Consistent with this phenomenon, the HSSs were associated with the subchondral pathologies, such as BML, SBC and SBA, and the TGF-β expression levels in the vasculature of the synovium in the patients, suggesting the presence of a relationship between histological synovitis and subchondral pathologies, and presumably synovial TGF-β
expression in patients with end-stage knee OA.

However, there are still many unsolved questions remaining, such as how to explain the relationship between synovial TGF-β and subchondral pathologies, such as BML, SBC and SBA, whether TGF-β is released when subchondral pathologies develop in subchondral lesions, and if so, how TGF-β in subchondral lesions is transferred to the joint, i.e., directly or indirectly (such as via the blood flow), or, if not, how BMLs in subchondral lesions induce TGF-β expression in the synovium. In addition, whether TGF-β expressed in the synovium in patients with end-stage knee OA is activated remains unclear. However, TGF-β is the present studies suggest that TGF-β is involved in the association between synovitis and the subchondral pathologies in patients with end-stage knee OA, although further investigation is required.

There were several limitations associated with the current study. As the present study is cross-sectional, the causal relationship between the MRI-detected OA-related structural changes and histological synovitis is still obscure. In this context, the results obtained in this study may be understood to be indirect evidence. The MRI-based WORMS assessment was performed by non-expert readers with limited experience in the semi-quantitative MRI analysis of knee OA features. To overcome this limitation, we calculated the inter-observer reproducibility for the MRI evaluation between the observers and the musculoskeletal
radiologist, as described in the Method section.

In conclusion, the presence of BML, SBC and SBA, but not other MRI-detected structural changes, was associated with local histological synovitis in end-stage knee OA patients who received TKA.
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Contributions

AY, HK and MI conceived and designed the study. HK, RS, SH, KOK, MK, IF, YS, MT, YS, YT, HI and MI collected and registered patients data. AY, HK, LL, LN, RS, SH, MK, YS, MT, SA, KAK and MI had the major role in analysis and interpretation of the data, and contributed to drafting the report. KAK also supervised the statistical analysis. All authors have read and approved the final manuscript.
Role of the funding source

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Competing interests

All authors declare that they have no competing interests.
References


The characteristics of the patients in this study

<table>
<thead>
<tr>
<th>Subject (n)</th>
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</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>71.8 (6.9)</td>
</tr>
<tr>
<td>Gender (F / M)</td>
<td>35 / 5</td>
</tr>
<tr>
<td>JKOM score (Range; 0 - 100)</td>
<td>49.2 (20.0)</td>
</tr>
<tr>
<td>Pain VAS score (0 - 100)</td>
<td>61.2 (26.9)</td>
</tr>
<tr>
<td>FTA (º)</td>
<td>185.0 (5.6)</td>
</tr>
<tr>
<td>WORMS (0 - 332)</td>
<td>145.0 (27.0)</td>
</tr>
<tr>
<td>Cartilage morphology (0 - 84)</td>
<td>61.1 (8.6)</td>
</tr>
<tr>
<td>BML (0 - 45)</td>
<td>16.1 (9.3)</td>
</tr>
<tr>
<td>SBC (0 - 45)</td>
<td>2.9 (3.0)</td>
</tr>
<tr>
<td>SBA (0 - 42)</td>
<td>4.3 (3.2)</td>
</tr>
<tr>
<td>Osteophyte (0 - 98)</td>
<td>48.0 (13.7)</td>
</tr>
<tr>
<td>Medial (0 – 6)</td>
<td>5.5 (0.5)</td>
</tr>
<tr>
<td>Lateral (0 – 6)</td>
<td>3.8 (1.0)</td>
</tr>
<tr>
<td>Synovitis (Range; 0 – 3)</td>
<td>2.0 (0.9)</td>
</tr>
<tr>
<td>HSS (0 – 15)</td>
<td>5.5 (0.8)</td>
</tr>
</tbody>
</table>

The data indicates the means (SD). JKOM: Japanese knee osteoarthritis measure, VAS: visual analog scale, FTA: femoro-tibial angle (lateral FTA; 185 degrees indicate 5 degrees of anatomical varus), WORMS: whole-organ magnetic resonance imaging score, BML: bone marrow lesion, SBC: subchondral bone cyst, SBA: subchondral bone attrition, HSS: histological synovitis score.
Table 2

Correlation between the total HSS and the WORMS in patients with end-stage knee OA receiving TKA

<table>
<thead>
<tr>
<th>HSS</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilage morphology</td>
<td>-0.006</td>
<td>0.97</td>
</tr>
<tr>
<td>BML</td>
<td>0.325</td>
<td>0.04*</td>
</tr>
<tr>
<td>SBC</td>
<td>0.350</td>
<td>0.03*</td>
</tr>
<tr>
<td>SBA</td>
<td>0.482</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Osteophyte</td>
<td>-0.100</td>
<td>0.54</td>
</tr>
<tr>
<td>Medial</td>
<td>0.155</td>
<td>0.34</td>
</tr>
<tr>
<td>Lateral</td>
<td>0.266</td>
<td>0.10</td>
</tr>
<tr>
<td>Synovitis</td>
<td>0.358</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

HSS: histological synovitis score, WORMS: whole-organ magnetic resonance imaging score, BML: bone marrow lesion, SBC: subchondral bone cyst, SBA: subchondral bone attrition. * indicates $p<0.05$. 
Table 3

Correlation between the total HSSs and the inflammatory cytokines and growth factor in patients with end-stage knee OA receiving TKA

<table>
<thead>
<tr>
<th>HSS</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lining layer</td>
<td>0.223</td>
<td>0.19</td>
</tr>
<tr>
<td>Sublining layer</td>
<td>0.277</td>
<td>0.10</td>
</tr>
<tr>
<td>Lining layer</td>
<td>0.018</td>
<td>0.92</td>
</tr>
<tr>
<td>COX-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sublining layer</td>
<td>0.080</td>
<td>0.67</td>
</tr>
<tr>
<td>Vasculature</td>
<td>0.231</td>
<td>0.22</td>
</tr>
<tr>
<td>Lining layer</td>
<td>0.043</td>
<td>0.81</td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sublining layer</td>
<td>0.211</td>
<td>0.24</td>
</tr>
<tr>
<td>Vasculature</td>
<td>0.122</td>
<td>0.50</td>
</tr>
<tr>
<td>Lining layer</td>
<td>0.073</td>
<td>0.70</td>
</tr>
<tr>
<td>TGF-β</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sublining layer</td>
<td>0.151</td>
<td>0.43</td>
</tr>
<tr>
<td>Vasculature</td>
<td>0.394</td>
<td>0.03*</td>
</tr>
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</table>

HSS: histological synovitis score, IL-1β; interleukin-1β, COX-2; cyclo-oxygenase (COX)-2, TNF-α; tumor necrosis factor-α, TGF-β; transforming growth factor, *p<0.05
Figure 1. Association between the HSS and the BML score (A), SBC score (B) and SBA score (C) in patients with end-stage knee OA receiving TKA.

The sagittal T2-weighted MR image (D, E and F) and the histological sections (G, H and I) of the three representative cases (J, K and L, respectively) those showed the presence of BML, SBC and SBA.

J: Cartilage loss: grade 6 in MFc (arrow with head) and MTc, grade 5 in MFa and MTa, grade 4 in MFp and MTp, BML: grade 3 in MTa, grade 2 in MFc (arrow head), SBC: grade 1 in MFc (thin arrow), SBA: grade 1 in MTc (thick arrow), osteophyte: grade 7 in MFa (open arrow head), grade 5 in MFp, MTa and MTp, meniscus: grade 4 in the medial meniscus (open arrow).

K: Cartilage loss: grade 6 in MFa, MFc, MTa and MTc, grade 5 in MFp (arrow with head) and MTp, BML: grade 3 in MFa, MFc (arrow head), MTa and MTc, grade 2 in MTp, SBC: grade 1 in MFa and MFc (thin arrow), SBA: grade 2 in MTc (thick arrow), osteophyte: grade 7 in MFa (open arrow head) and MFp, grade 6 in MTa, grade 5 in MTp, meniscus: grade 3 in the medial meniscus (open arrow), effusion: grade 1 (star).

L: Cartilage loss: grade 6 in MFc (arrow with head), MFp and MTc, grade 4 in MFa and MTa, BML: grade 3 in MFa, MFc (arrow head), MFp, MTa, MTc and MTp, SBC: grade 3 in MFc (thin arrow), grade 2 in MFp, SBA: grade 3 in MFc and MTc (thick arrow), osteophyte: grade 4 in MTa (open arrow head) and MTp, grade 2 in MFa, meniscus: grade 3 in the medial meniscus (open arrow), effusion: grade 3 (star). BML: bone marrow lesion, SBC: subchondral bone cyst, SBA: subchondral bone attrition, HSS: histological synovitis score, TKA: total knee arthroplasty.
Figure 1