Clinical Rheumatology (2021) 40:2007–2012
https://doi.org/10.1007/s10067-020-05453-1

ORIGINAL ARTICLE

Pathological features of established osteoarthritis with hydrathrosis are similar to rheumatoid arthritis

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Received: 16 September 2020 / Revised: 16 September 2020 / Accepted: 6 October 2020 / Published online: 8 October 2020

Abstract

Objectives The prevalence of rheumatoid arthritis (RA) and knee osteoarthritis (OA) is increasing with our aging society. Some reports suggest that OA with effusion synovitis develops into RA and early OA patients with effusion are pathologically similar to those with RA. The purpose of this study was to examine the relationship between histological features of established knee OA with or without effusion and RA.

Methods Seventy-nine patients in which synovial specimens were obtained during total knee arthroplasty were included. Patients were divided into an RA group, OA with effusion (OA+) group, and OA without effusion (OA−) group. The Rooney synovitis score and serum matrix metalloproteinase (MMP)-3 levels were compared among groups. We also examined the correlation between the Rooney synovitis score and its sub-scores with MMP-3 levels.

Results The total Rooney score was significantly higher in the RA group than in the OA+ and OA− groups (25.4 vs 17.1, $p < 0.01$; 25.4 vs 13.5, $p < 0.001$, respectively). This score also was significantly higher in the OA+ group than in the OA− group ($p < 0.05$). The proliferating blood vessels score, perivascular infiltrates of lymphocytes score, focal aggregates of lymphocytes score, and diffuse infiltrates of lymphocytes score were significantly higher in the RA group than in the OA− group (7.05 vs 3.29, 4.95 vs 3.43, 3.29 vs 1.46, and 2.26 vs 1.18, respectively; $p < 0.05$), but not compared with the OA+ group. The total Rooney score demonstrated a significantly positive correlation with serum MMP-3 levels in the RA group ($r = 0.61$; 95% CI: 0.28 to 0.81; $p < 0.01$) and in the OA+ group ($r = 0.57$; 95% CI: 0.24 to 0.78; $p < 0.01$).

Conclusions Previous reports showed the histological similarity between RA and early OA with effusion. We confirmed this histological similarity, in particular the distribution of lymphocytes, between RA and established OA with effusion. It is possible that cases diagnosed as OA with effusion might progress to overt RA.

Key Points:
• *Histological similarity was observed between RA and established OA with effusion.*

Keywords Histopathological score · Rheumatoid arthritis · Serum MMP-3 · Synovitis

Introduction

The prevalence of rheumatoid arthritis (RA) is increasing with the aging of the population. The residual life time risk of RA developing in the USA in people over 60 years old was reported to be 2.04% in women and 1.11% in men [1]. Elderly onset rheumatoid arthritis (EORA) is defined as RA that develops after the age of 60 years [2]. The characteristic of EORA is joint pain that appears in the large joints such as the knee or shoulder. At diagnosis of EORA, there are many cases with knee osteoarthritis (OA) or hand OA [3, 4].

The prevalence of knee OA with Kellgren/Lawrence (KL) grade ≥ 2 was reported to be 47% in men and 70.2% in women more than 60 years old in a Japanese large observational cohort [5]. The prevalence of knee OA is expected to increase further due to the influence of a hyper-aging society. Synovial fluid effusion is one characteristic of knee OA, as it is in the

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diagnostic criteria [6]. Some reports suggest that knee OA with effusion synovitis develops into RA [7–9]. Furthermore, early OA patients with effusion are pathologically similar to patients with RA and require careful follow-up [9]. However, little is known about the relationship between histological feature of established knee OA with effusion and RA. The purpose of the present study was to examine the relationship between histological features of established high-grade knee OA, with or without effusion, and RA.

Patients and methods

This study was approved by our institutional review board (application No. 1222).

Design and patients

This study was a retrospective, single-center review of the records of patients who underwent primary total knee arthroplasty (TKA). From 2010 to 2015, 79 patients in which synovial specimens were obtained during TKA were enrolled. All patients fulfilled KL grade ≥ 3 status. The sample included 24 patients with RA diagnosed according to the American College of Rheumatology criteria [10] and 55 patients with OA [6]. All OA patients were older than 60 years. The OA patients were divided into those with effusion (OA+) and those without effusion (OA−). Positive effusion was defined as 5 ml or more of synovial fluid and was confirmed by operative findings. Preoperative serum matrix metalloproteinase (MMP)-3 data were collected from an electronic medical record.

Histopathological assessment

Synovial tissues were harvested from the knee joints at surgery and fixed in 4% paraformaldehyde. To avoid sampling error, specimens were limited to the suprapatellar bursa. Histological synovitis in hematoxylin and eosin (H-E)-stained sections was graded using the Rooney synovitis score, which contains six sub-scores of synoviocyte hyperplasia (SH), fibrosis (FI), proliferating blood vessels (PBV), perivascular infiltrates of lymphocytes (PIL), focal aggregates of lymphocytes (FAL), and diffuse infiltrates of lymphocytes (DIL). Each was scored from 0 to 10, and the sum provided the synovitis score from 0 to 60 [11]. The evaluation of the Rooney score was performed by two pathologists.

Statistical analysis

Data were sorted, coded, and entered into a Microsoft Excel spreadsheet for evaluation using GraphPad Prism for Windows, version 7.0 (GraphPad Software, San Diego, CA, USA). Data were analyzed using a Mann-Whitney *U* test, Kruskal-Wallis test, or chi-square test to determine significant differences. Correlations between the Rooney score and serum MMP-3 levels were determined using Pearson correlation coefficients. $p < 0.05$ was considered to be statistically significant.

Results

Patient's background

There was no significant difference in age among the groups (RA,70.3 vs OA+,75.1 vs OA−,76.3; $p = 0.08$). No significant differences were found in the percentage of female patients (87.5% vs 81.5% vs 89.3%; $p = 0.68$) or KL grade among the groups. There was a significant difference in c-reactive protein (CRP) among the RA, OA+, and OA− groups (0.75 vs 0.33 vs 0.14; $p < 0.001$). The mean disease duration for the RA group was 11.1 years, and the mean disease activity score using 28 joint count-CRP (DAS28-CRP) was 4.04 (range, 2.76–5.74) preoperatively (Table 1).

Table 1 Patient characteristics

Variable	RA ($n = 24$)	OA with effusion (OA+, $n = 27$)	OA without effusion (OA−, $n = 28$)	*p*
Age (years)	70.3 ± 10.3	75.1 ± 6.5	76.3 ± 6.0	0.08
Female (%)	87.5	81.5	89.3	0.68
Disease duration (years), (range)	11.1 (2–45)	–	–	–
CRP (mg/dL)	0.75 ± 0.96	0.33 ± 0.56	0.14 ± 0.06	< 0.001
DAS28-CRP (range)	4.04 (2.76–5.74)	–	–	–
KL grade (3/4)	11/13	12/15	14/14	0.91

Data are mean ± standard deviation unless otherwise indicated

RA rheumatoid arthritis, *OA* osteoarthritis, *CRP* C-reactive protein, *DAS28* disease activity score using 28 joint count, *KL* Kellgren-Lawrence

Comparison of Rooney score in each groups

The total Rooney score was significantly higher in the RA group than in the OA+ and OA− groups (25.4 vs 17.1, $p < 0.01$; 25.4 vs 13.5, $p < 0.001$, respectively). This score also was significantly higher in the OA+ group than in the OA− group (17.1 vs 13.5; $p < 0.05$) (Fig. 1a). Comparing the components of the Rooney score in each group, the SH score was significantly higher in the OA+ group than in the RA group (2.56 vs 1.90; $p < 0.05$), but there was no significant difference between the other pairwise combinations of groups (Fig. 1b). The FI score was significantly higher in the RA group than in the OA+ and OA− groups (7.05 vs 3.70, $p < 0.001$; 7.05 vs 3.29, $p < 0.001$, respectively). However, there was no significant difference between the OA+ and OA− groups (3.70 vs 3.29; $p = 0.43$) (Fig. 1c). The PBV score was significantly higher in the RA group than in the OA− group (4.95 vs 3.4; $p < 0.05$), but there was no significant difference between the other combinations of groups (Fig. 1d). The PIL score was significantly higher in the RA group than in the OA− group (3.29 vs 1.46; $p < 0.01$), but there was no significant difference between the other groups

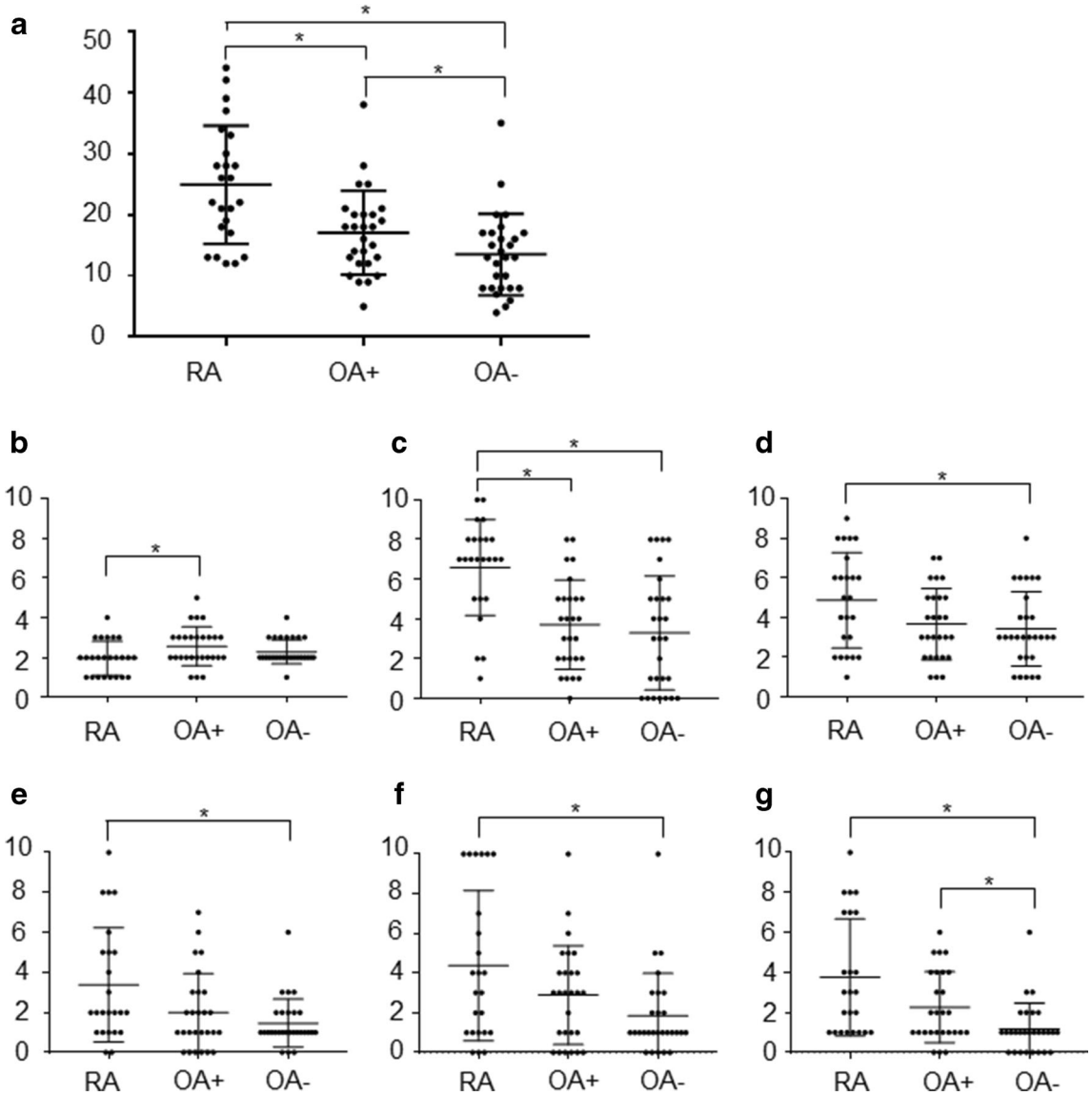

Fig. 1 Comparison of Rooney score in each groups. The total Rooney score was significantly higher in the RA group than in the OA+ and OA− groups (25.4 vs 17.1, $p < 0.01$; 25.4 vs 13.5; $^*p < 0.001$, respectively). This score was also significantly higher in the OA+ group than in the OA − group (17.1 vs 13.5; $^*p < 0.05$) (**a**). SH score was significantly higher in the OA+ group than in the RA group (2.56 vs 1.90; $p < 0.05$) (**b**). The PBV score (**c**), PIL score (**d**), FAL score (**e**), and DIL score (**f**) were significantly higher in the RA group than in the OA− group (7.05 vs 3.29, 4.95 vs 3.43, 3.29 vs 1.46, and 2.26 vs 1.18, respectively; $^*p < 0.05$). The FI score (**c**) also was significantly higher in the RA group than in the OA+ group (7.05 vs 3.70; $p < 0.001$). The DIL score (**g**) was significantly lower in the OA− group than in the OA+ group (1.18 vs 2.26; $p < 0.05$)

(Fig. 1e). The FAL score was significantly higher in the RA group than in the OA− group (4.43 vs 1.86; $p < 0.05$), but there was no significant difference between the other groups (Fig. 1f). The DIL score was significantly lower in the OA− group than in the RA and OA+ groups (1.18 vs 3.81, $p < 0.001$; 1.18 vs 2.26, $p < 0.05$, respectively). However, there was no significant difference between the RA group and the OA+ group (3.81 vs 2.26; $p = 0.08$) (Fig. 1g).

Comparison of serum MMP-3 levels in each group

Serum MMP-3 levels were significantly lower in the OA− group than in the RA and OA+ groups (54.6 vs 282.3, $p < 0.01$; 54.6 vs 147.1, $p < 0.01$, respectively). No significant difference was observed between the RA and OA+ groups (282.3 vs 147.1; $p = 0.21$) (Fig. 2).

Correlation between Rooney score and serum MMP-3 levels in each group

The total Rooney score was positively and significantly correlated with serum MMP-3 levels in the RA group ($r = 0.61$; 95% CI: 0.28 to 0.81; $p < 0.01$) and in the OA+ group ($r = 0.57$; 95% CI: 0.24 to 0.78; $p < 0.01$). However, there was no correlation between total Rooney score and serum MMP-3 levels in the OA− group ($r = -0.05$; 95% CI: −0.42 to 0.76; $p = 0.79$) (Table 2). Furthermore, the correlations between the components of the Rooney score and serum MMP-3 levels were examined. In the RA group, there was a significant correlation between serum MMP-3 levels and PIL ($r = 0.71$; 95% CI: 0.43 to 0.86; $p < 0.01$), FAL ($r = 0.48$; 95% CI: 0.09 to 0.74; $p < 0.05$), and DIL ($r = 0.59$; 95% CI: 0.25to 0.80; $p < 0.01$). However, there was no correlation between serum MMP-3 levels and SH ($r = 0.37$; 95% CI: −0.04 to 0.67; $p = 0.08$), FI ($r = -0.36$; 95% CI: −0.67 to 0.05; $p = 0.08$), or PBV ($r = 0.38$; 95% CI: −0.02 to 0.68; $p = 0.07$) (Table 3). In the OA+ group, there was a significant correlation between serum MMP-3 levels and PIL ($r = 0.58$; 95% CI: 0.25 to 0.79; $p < 0.01$), and with FAL ($r = 0.58$; 95% CI: 0.25 to 0.79; $p < 0.05$). However, there was no correlation between serum MMP-3 levels and SH ($r = -0.11$; 95% CI: −0.47 to 0.28; $p = 0.59$), FI ($r = 0.16$; 95% CI: −0.24 to 0.51; $p = 0.44$), PBV ($r = 0.26$; 95% CI: −0.13 to 0.58; $p = 0.19$), or DIL ($r = 0.37$; 95% CI: −0.01 to 0.66; $p = 0.06$) (Table 3). In the OA− group, there was no correlation between serum MMP-3 levels and any of the components of the Rooney score (Table 3).

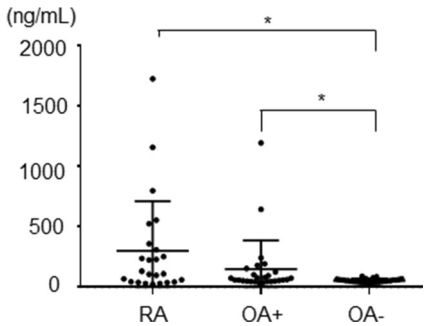

Fig. 2 Comparison of serum MMP-3 levels in each group. Serum MMP-3 levels were significantly lower in the OA− group than in the RA and OA+ groups (54.6 vs 282.3, p < 0.01; 54.6 vs 147.1; p < 0.01, respectively)

Table 2 Correlation between total Rooney score and serum MMP-3 levels

	r	*p*
RA	0.61 (0.28 to 0.81)	< 0.01
OA with effusion (OA+)	0.57 (0.24 to 0.78)	< 0.01
OA without effusion (OA−)	− 0.05 (− 0.42 to 0.33)	0.79

RA rheumatoid arthritis, *OA* osteoarthritis

Discussion

This study investigated the relationship between histological features of established OA with or without hydrathrosis and RA. The results of the current study indicated that a similarity of pathological features was found between OA with effusion and RA, especially in terms of lymphocyte distribution. To the best of our knowledge, this is the first study to examine the relationship between histological features of long-standing OA with effusion and RA.

The characteristic histopathological features of RA synovitis were summarized previously as proliferation of the synovial cells, presence of non-foreign body-type giant cells, presence of lymphoid follicles with the formation of a germinal center, infiltration of plasma cells in the synovial stroma, proliferation of granulation tissue characterized by mesenchymoid transformation, presence of polymerized fibrin, and presence of hemosiderosis [12]. On the other hand, the characteristic histopathological features of OA synovitis were characterized as synovial lining hyperplasia, infiltration of macrophages and lymphocytes, neoangiogenesis, and fibrosis [13]. There are many pathological similarities between RA and OA. The results of our study indicated a pathological approximation of RA and OA with effusion and PBV, PIL, FAL, and DIL. However, there was a significant difference between RA and OA without effusion for the same markers. The presence of effusion might cause a pathological difference even between the OA. In particular, a significant difference was found between OA with effusion and without effusion in terms of DIL. It is necessary to pay attention to the location of lymphocyte aggregation.

Serum levels of MMP-3 were reported to be a surrogate marker of synovitis in RA [14, 15]. No statistically significant

Table 3 Correlation between Rooney score components and serum MMP-3 levels

	RA		OA with effusion (OA+)		OA without effusion (OA−)	
	r	*p*	*r*	*p*	*r*	*p*
SH	0.37 (− 0.04 to 0.67)	0.08	− 0.11 (− 0.47 to 0.28)	0.59	− 0.18 (− 0.51 to 0.21)	0.37
FI	− 0.36 (− 0.67 to 0.05)	0.08	0.16 (− 0.24 to 0.51)	0.44	− 0.06 (− 0.43 to 0.32)	0.75
PBV	0.38 (− 0.02 to 0.68)	0.07	0.26 (− 0.13 to 0.58)	0.19	− 0.33 (− 0.63 to 0.05)	0.08
PIL	0.71 (0.43 to 0.86)	*< 0.01*	0.58 (0.25 to 0.79)	*< 0.01*	0.20 (− 0.19 to 0.53)	0.32
FAL	0.48 (0.09 to 0.74)	*< 0.05*	0.58 (0.25 to 0.79)	*< 0.01*	0.07 (− 0.31 to 0.43)	0.71
DIL	0.59 (0.25 to 0.80)	*< 0.01*	0.37 (− 0.01 to 0.66)	0.06	0.13 (− 0.26 to 0.48)	0.52

Statistically significant values are pointed by italic style

Data are coefficient of correlation and 95% confidence interval unless otherwise indicated

RA rheumatoid arthritis, *OA* osteoarthritis, *SH* synoviocyte hyperplasia, *FI* fibrosis, *PBV* proliferating blood vessels, *PIL* perivascular infiltrates of lymphocytes, *FAL* focal aggregates of lymphocytes, *DIL* diffuse infiltrates of lymphocytes

correlations between serum MMP-3 levels and Rooney score were reported previously [16], but there was a significant correlation between serum MMP-3 and Rooney score in the RA group and in the OA+ group in this study. Although the previous report did not mention the presence of effusion, this difference might be due to the effects of effusion synovitis. In addition, it was confirmed that PIL and FAL correlated with serum MMP-3 levels in both RA and OA+ groups. It has been reported that the type of RA with diffuse infiltrate of lymphocytes is highly correlated with serum MMP-3 levels [17]. It was suggested that the existence of lymphocytes in synovitis was more important than the difference between RA and OA for serum MMP-3 levels.

This study had some limitations. First, we could not examine the presence of effusion in the RA group because of the inaccurate data collection. Baeten et al. reported that histological scores were significantly higher in mean lining thickness, vascularity, infiltration, lymphocyte, and plasma cells in RA with effusion than in RA without effusion [18], but they did not report Rooney scores. Next, we did not examine the presence of serum rheumatoid factor and anti-citrullinated protein antibody in all OA groups. In fact, there was a case of RA in the OA+ group 2 years after TKA. There is a possibility that more cases might develop into RA in the future.

In conclusion, previous reports showed the histological similarity between RA and early OA with effusion. The significant results in the present study support the histological similarity, especially the distribution of lymphocytes, between RA and established OA with effusion. It is possible that cases diagnosed as OA with effusion might progress to overt RA.

Compliance with ethical standards

This study was approved by our institutional review board (application No. 1222).

Disclosures None.

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