Table 1 Characteristics of patients with OA and RA

	OA (n = 23)	RA (n = 30)
Male/female, n	2/21	6/24
Age, mean ± SD (range, years)	76.6 ± 5.8 (64–84)	69.4 ± 8.1 (55–83)
Disease duration, mean ± SD (years)	10.7 ± 5.1	16.3 ± 9.1
CRP, mean ± SD (mg/dl)	0.16 ± 0.30	1.43 ± 1.21
DAS28-CRP, mean ± SD	-	3.74 ± 0.84
Medications		
Prednisolone, n (%)	NA	17 (56.7)
Methotrexate, n (%)	NA	15 (50.0)
Sulfasalazine, n (%)	NA	7 (23.3)
Bucillamine, n (%)	NA	6 (20.0)
Cyclosporine, n (%)	NA	3 (10.0)
Actarit, n (%)	NA	1 (3.3)
TNF-α blockade, n (%)	NA	4 (13.3)

n, number; OA, osteoarthritis; RA, rheumatoid arthritis; SD, standard deviation; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; NA, not applicable.

Quantification of Sema3A immunostaining

Tissue sections immunostained with anti-Sema3A antibody were analyzed for 12 patients with OA and 12 patients with RA. The total immunostaining intensity in the lining layer was measured using a BZ-9000 microscope (Keyence, Osaka, Japan) equipped with Dynamic Cell count software BZ-H1C (Keyence). Immunostaining intensity per unit was calculated as described previously [34].

Quantitative real-time polymerase chain reaction (qPCR)

Total RNA was extracted from synovial tissues using an Illustra RNA spin Mini Kit (GE Healthcare, Buckinghamshire, UK) according to the manufacturer's instructions. RNA was reversed transcribed into cDNA using a PrimeScript RT Reagent Kit (Takara Bio, Ohtsu, Japan). The cDNA synthesized from 1 μg of total RNA was used as the template in each reaction. qPCR analysis was performed using an Applied Biosystems 7900HT Fast Real-time PCR system (Applied Biosystems LLC) based on the TaqMan® PCR manufacturer's protocol. The assay was performed in triplicate in optical 96-well reaction plates covered with optical adhesive cover in a volume of 10 μl containing 0.5 μl Taqman Gene Expression Assay 20X for human *Sema3A* (assay ID Hs01085496_m1, GenBank accession number NM_006080, Applied Biosystems LLC), *VEGF-A* (assay ID Hs00173626_m1, GenBank accession number NG_008732, Applied Biosystems LLC), *NRP1* (assay ID Hs00826128_m1, GenBank accession number NM_003873; Applied Biosystems LLC) and *β-actin* (assay ID 4326315E, GenBank accession number NM_001101; Applied Biosystems LLC), 5 μl Taqman Fast Advanced Master Mix 2X, 2 μl cDNA template and 2.5 μl RNase-free water. The default ABI 7900HT amplification conditions were 20 sec at 95°C, followed by 1 sec at 95°C and 20 sec at 60°C for 40 cycles. A standard curve, derived from known serial dilutions of RA synovial tissue, was constructed to

Table 2 Rooney's inflammation scoring system for patients with rheumatoid arthritis

	Score										
Histologic feature	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Synoviocyte hyperplasia[a]	1	2	3	4	5	6	7	8	9	10	>10
Fibrosis[b]	<10	<15	<20	<25	<30	<40	<50	<60	<70	<80	≥80
Proliferating blood vessels[c]	0–3	4–5	6–7	8–9	10–11	12–13	14–15	16–17	18–19	20–22	>22
Perivascular infiltrates of lymphocytes[d]	<5	10	20	30	40	50	60	70	80	90	100
Focal aggregates of lymphocytes[e]	<11	15	20	25	30	35	40	45	50	55	>55
Diffuse infiltrates of lymphocytes[f]	0	10	20	30	40	50	60	70	80	90	100

[a]A normal synoviocyte monolayer was scored as 0. The score was increased as the synoviocyte lining layer increased in depth. [b]Sections containing < 10% fibrous tissue in the sublining layers were scored as 0. The score increased as the percentage of fibrosis in the section increased. [c]Three or fewer vessels per high power field (HPF) were scored as 0. The score increased as the number of vessels per HPF increased. [d]When no lymphocytes were observed around vessels, it was scored as 0. The score increased as the percentage of vessels surrounded by lymphocytes increased. Subsequently, the diameter of the perivascular lymphocytes was graded as mild = 2–4 cells in diameter, moderate = 5–7 cells in diameter, and severe = 8–10 cells in diameter. Where the perivascular lymphocytes were considered mild or severe, the original score was lowered by 1 point or raised by 1 point, respectively. [e]Absence of focal aggregates of lymphocytes, which exceeded 10 cells in diameter, were scored as 0. The score increased as the cell numbers in the diameter of the focal aggregates increased. [f]An estimate was made of the percentage of cells per HPF that were lymphocytes. The score increased as the percentage of lymphocytes increased.

calculate arbitrary values of mRNA levels and to correct for differences in primer efficiencies. The obtained data were standardized using the reference gene, *β-actin*.

Double-staining Immunofluorescence

Synovial tissue specimens embedded in Optimum Cutting Temperature compound (Sakura Finetek Japan, Tokyo, Japan) were sectioned (5 μm thick). The sections were then fixed in cold acetone for 5 min at 4°C and rinsed in phosphate buffered saline (PBS). To eliminate nonspecific protein binding, the samples were incubated with 10% normal goat serum for 30 min at room temperature. The samples were incubated with rabbit anti-NRP1 polyclonal antibody (1:100; Santa Cruz Biotechnology) and mouse anti-CD20 monoclonal antibody (DAKO) overnight at 4°C. This was followed by incubation with Alexa 488-labeled goat anti-rabbit antibody (Applied Biosystems LLC, Foster City, CA, USA) and Alexa 594-labeled goat anti-mouse antibody (Applied Biosystems LLC) for 40 min at 37°C. Finally, the sections were mounted with aqueous mounting medium. The distributions were analyzed by confocal microscopy using a Zeiss LSM510 confocal laser microscope (Carl Zeiss, Oberkochen, Germany).

Statistical analysis

Statistical analyses were performed using SPSS 11.0 for Windows (SPSS Inc, Chicago, IL). The Mann–Whitney *U*-test and Spearman's rank correlation coefficient were used to test the differences. A p value < 0.05 was considered significant. We calculated a posterior power of this study using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007). All statistical powers in this study were greater than 80%.

Results

Sema3A, $VEGF_{165}$, NRP1 and CD3 expression in OA and RA synovial tissues

To investigate the involvement of Sema3A in RA pathogenesis, we performed immunohistochemical staining for Sema3A, $VEGF_{165}$ and NRP1 expression in serial synovial serial sections from RA and OA patients. HE staining demonstrated that synovial tissues from OA patients contained two layers, the lining and sublining layers (Figure 1A). Sema3A was mainly expressed in the lining layer and a small number of inflammatory cells were present in the sublining layer of OA samples (Figure 1B). This immunoreactive signal was abolished by the preincubation of anti-Sema3A antibody with the antigen peptide (Figure 1C), confirming the specificity of Sema3A immunostaining. In RA specimens, there was a marked increase in synovial tissue thickness of the lining layer caused by hyperplasia of synovial cells and numerous infiltrating inflammatory cells in the sublining layer (Figure 1D). The immunostaining signal of Sema3A in the hyperplastic lining layer was lower in RA tissues compared with OA samples (Figure 1E). Additionally, numerous inflammatory cells in the sublining layer expressed Sema3A. In OA and RA synovial tissues, $VEGF_{165}$ was expressed in the lining layer and in the inflammatory cells of the sublining layer (Figure 1G, J). The $VEGF_{165}$ expression density in the lining layer did not differ between RA and OA samples. NRP1, the shared receptor for Sema3A and $VEGF_{165}$, was expressed in synovial cells of the lining layer, along with inflammatory cells and vascular endothelial cells in the sublining layer. The NRP1 expression density in the lining layer of RA was not significantly different to that of OA (Figure 1H, K). The localization of Sema3A, $VEGF_{165}$, and NRP1 almost overlapped, suggesting that functional competition for Sema3A and $VEGF_{165}$ may influence these cells. To evaluate the infiltration of immune cells, sections were stained with anti-CD3 antibody, a marker for T cells and anti-CD20 antibody, a marker for B cells. While T cells (CD3) were sporadically localized in the sublining layer of OA specimens, the number of T cells was greater in RA synovial tissues (Figure 1I, L). B cells were also sporadically localized in the sublining layer of OA specimens and large numbers of B cells were observed in the lymphoid follicles of RA synovial tissues (Figure 1M, N). We quantified Sema3A-immunostaining signal in the lining layer of RA and OA specimens. Sema3A-immunostaining intensity per unit area of lining layer was significantly less in RA patients compared with OA (Figure 1O).

Expression of *Sema3A*, *VEGF-A* and *NRP1* mRNA and correlation with DAS28-CRP in RA

To confirm changes in Sema3A expression in RA, we examined mRNA expression levels in OA and RA joint specimens using qPCR analysis. To evaluate the expression levels of $VEGF_{165}$ we used *VEGF-A* primers in the qPCR experiments. *Sema3A* mRNA levels in synovial tissue samples were significantly lower in RA (mean expression level 1.80) than in OA (mean expression level 6.68; $p < 0.0001$; Figure 2A). The mRNA expression of *VEGF-A* or *NRP1* was not significantly different between RA and OA (Figure 2B, C). We also obtained similar results with $VEGF_{165}$ primer in preliminary study (Additional file 1: Figure S1A). We next examined the correlation of *Sema3A* expression levels with DAS28-CRP, the disease activity score for RA. A negative correlation was observed between *Sema3A* expression levels and DAS28-CRP ($R = -0.409$, $p = 0.025$; Figure 2D). This suggested that the reduction of *Sema3A* expression might augment the disease activity of RA. *VEGF-A* expression levels did not significantly correlate with DAS28-CRP ($R = 0.198$, $p = 0.295$; Figure 2E). We also found a negative correlation between *Sema3A/VEGF-A* ratios and DAS28-CRP ($R = -0.449$, $p = 0.013$; Figure 2F).

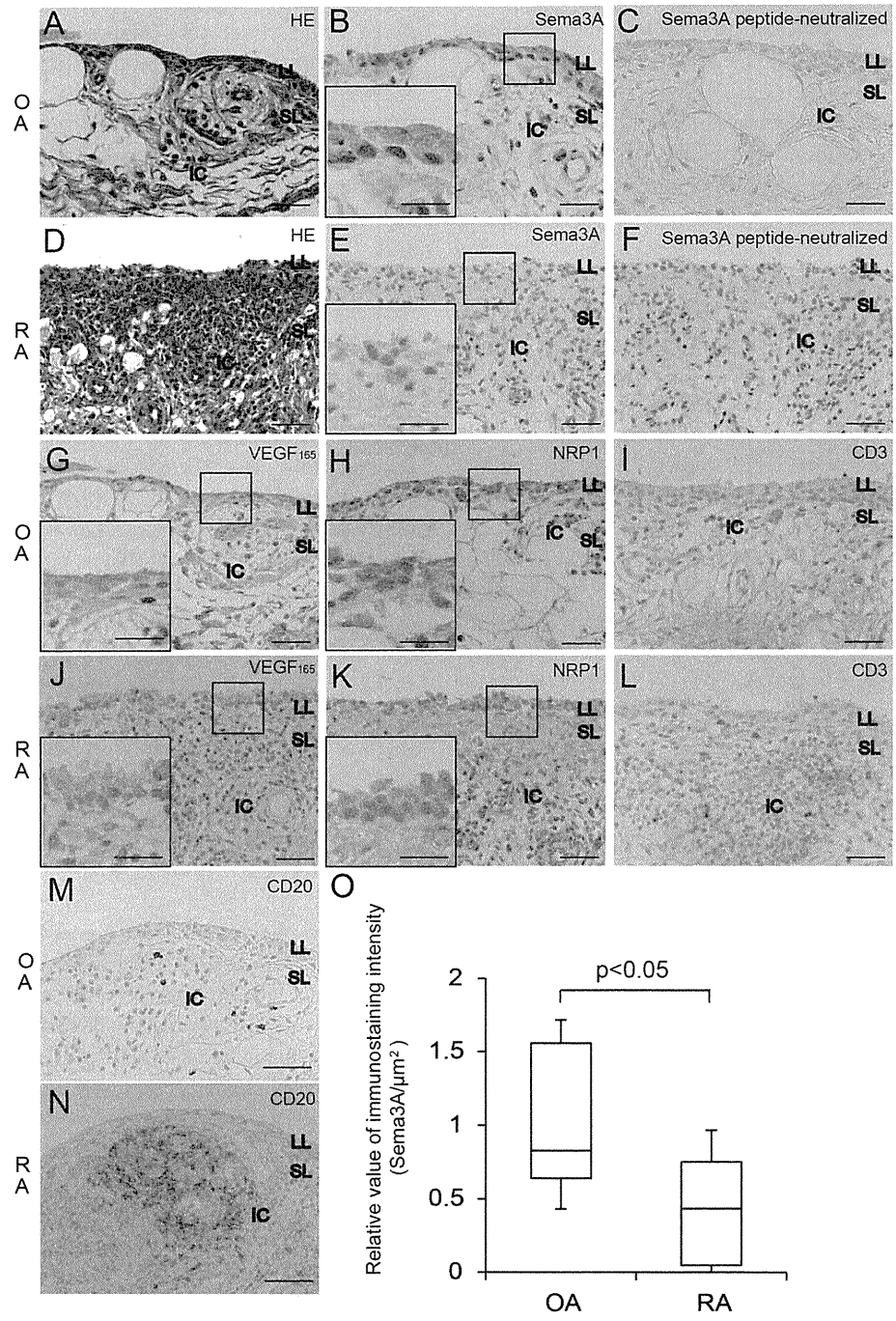

Figure 1 Histological/immunohistochemical analysis of Sema3A, NRP1, $VEGF_{165}$ and CD3 in OA and RA synovial tissue. Representative HE staining of OA (**A**) and RA (**D**) synovial tissues. OA synovial tissues contain lining (LL) and sublining (SL) layers. RA synovial tissues are marked by the hyperplasia of synovial tissues in the lining layer and numerous infiltrated inflammatory cells (IC) in the sublining layer. Sema3A expression was detected in the lining layer and inflammatory cells in the sublining layer of OA (**B**) and RA (**E**) synovial tissues. The density of the Sema3A signal in the lining layer was lower in RA than OA. Peptide-neutralized anti-Sema3A antibodies did not stain tissue sections from OA (**C**) and RA (**F**). NRP1 and $VEGF_{165}$ localized to the same areas as Sema3A in OA. $VEGF_{165}$ expression in the lining layer in RA tissues was similar with OA (**G, J**). The NRP1 expression level in the lining layer of RA was similar to OA (**H, K**). T cells (CD3) and B cells (CD20) were detected among inflammatory cells in the sublining layer of OA and RA synovial tissues (**I, L, M, N**). The numbers of T cells and B cells were higher in RA synovial tissues compared with OA. Sections were counterstained with hematoxylin. Scale bars = 50 μm in the whole image view and 25 μm in the magnified view. Immunostaining of lining layer Sema3A was significantly decreased in RA (n = 12) synovial tissues compared with OA (n = 12) subjects (**O**). Results are presented as relative values compared with OA subjects. The box plots demonstrate the 10th and 90th percentile (whiskers), the 25th and 75th percentile, and the median. P values were obtained using the Mann–Whitney *U*-test.

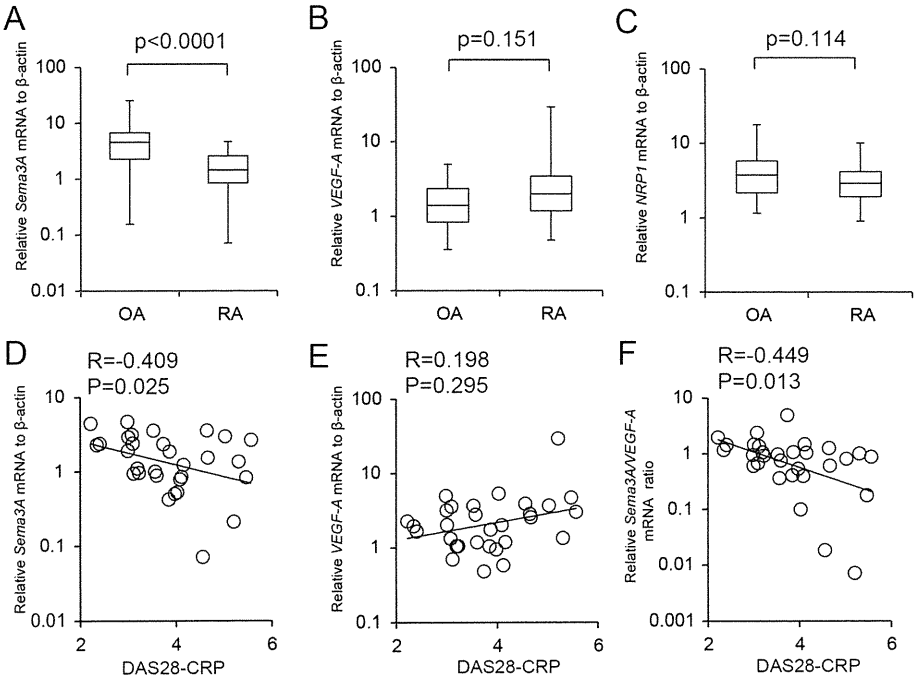

Figure 2 Expression of *Sema3A, VEGF-A* and *NRP1* mRNA in synovial tissues. Expression levels of *Sema3A*, *VEGF-A* and *NRP1* mRNA were measured using real-time PCR. The mRNA levels were normalized to the expression of *β-actin*. The box plots demonstrate the 10th and 90th percentile (whiskers), the 25th and 75th percentile, and the median. *Sema3A* mRNA levels were significantly decreased in RA (n = 30) synovial tissues compared with OA (n = 23) (**A**). *VEGF-A* and *NRP1* mRNA levels were not significantly altered (**B, C**). Correlation of *Sema3A* mRNA levels and DAS28-CRP (**D**); *VEGF-A* mRNA levels and DAS28-CRP (**E**); and *Sema3A/VEGF-A* mRNA levels and DAS28-CRP (**F**). P values were obtained using the Mann–Whitney *U*-test. were examined using Spearman's rank correlation coefficient.

Correlation of *Sema3A* mRNA levels with histological features in RA synovial tissues

To confirm the inverse correlation of *Sema3A* mRNA expression levels and RA disease activity, we compared the relative *Sema3A* mRNA expression levels with histological parameters of RA synovial tissues. This included the degree of synovial hyperplasia, fibrosis, number of blood vessels present, perivascular infiltrates of lymphocytes, focal aggregates of lymphocytes and diffuse infiltrates of lymphocytes. No significant correlation between *Sema3A* expression and synovial hyperplasia, fibrosis or the number of blood vessels was observed (Figure 3A–C). In contrast, perivascular infiltrates of lymphocytes, focal aggregates of lymphocytes and diffuse infiltrates of lymphocytes significantly correlated with *Sema3A* mRNA expression levels ($R = -0.506$, $p = 0.004$; $R = -0.501$, $p = 0.005$; $R = -0.536$, $p=0.002$ respectively; Figure 3D–F). These results indicated that *Sema3A* mRNA reduction was mainly associated with immune reactions in the synovial tissue from RA patients.

Expression of NRP1 in CD20-positive B cells in lymphocyte aggregates

Histological scores and *Sema3A* expression levels revealed that a decrease in Sema3A augmented focal aggregates of lymphocytes. To examine the cell types of NRP1-positive inflammatory cells, we stained sequential tissue sections with markers for T cells (CD3) and B cells (CD20). NRP1 was abundantly expressed in the inflammatory cells of lymphoid follicles (Figure 4A). In RA synovium, T cells, B cells and dendritic cells [35] can be arranged in sophisticated organizations that resemble the microstructures usually formed in secondary lymphoid organs. Interestingly, NRP1-expressing dendritic cells also exist in the lymphoid follicle/lymphocyte focal aggregates. Immunohistochemical staining of sequential slices from the lymphoid follicles showed that NRP1-positive cells also expressed CD3 or CD20 (Figure 4B, C). Since lymphoid follicles were mainly composed of B cells [36], we also performed double immunofluorescence staining of NRP1 and CD20. The NRP1 positive signal colocalized with the CD20 positive signal in the inflammatory cells of lymphocyte aggregates (Figure 4D-F).

Discussion

It has been suggested that abnormalities of the immune system play an important role in the pathogenesis of chronic inflammatory conditions such as RA. This study revealed *Sema3A* expression levels significantly correlated with the histological score of perivascular infiltrates of lymphocytes, focal aggregates of lymphocytes and diffuse infiltrates of lymphocytes. Sema3A is involved in

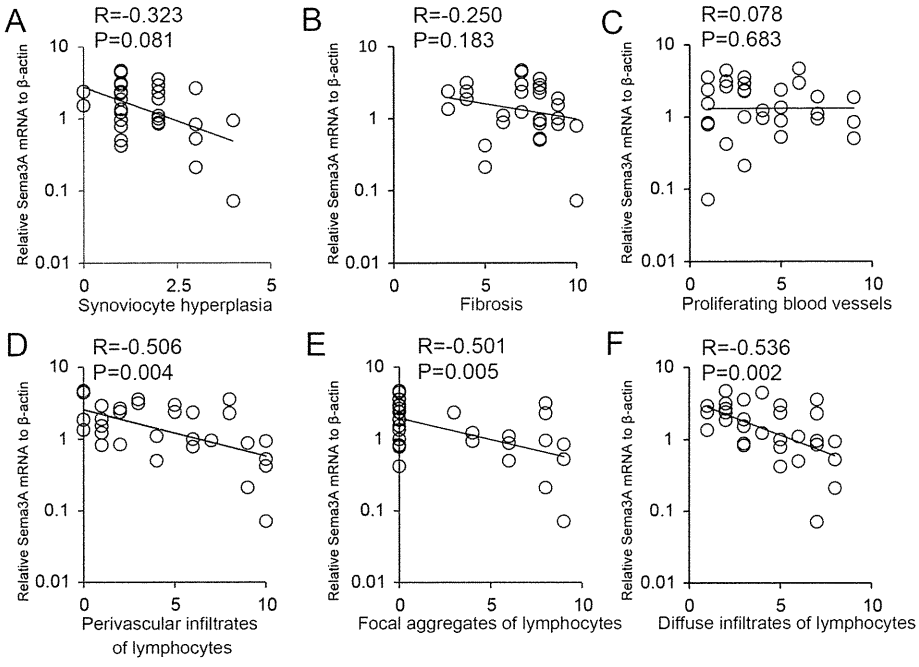

Figure 3 Expression levels of *Sema3A* mRNA correlate with histological features in RA synovial tissues. Correlations between *Sema3A* mRNA expression levels and histological parameters of RA synovial tissues were assessed. Histological parameters were scored separately on a scale of 0–10 according to Rooney's inflammation scoring system. Correlation of *Sema3A* mRNA levels and synoviocyte hyperplasia (**A**); *Sema3A* mRNA levels and fibrosis (**B**); *Sema3A* mRNA levels and proliferating blood vessels (**C**); *Sema3A* mRNA levels and perivascular infiltrates of lymphocytes (**D**); *Sema3A* mRNA levels and focal aggregates of lymphocytes (**E**); and *Sema3A* mRNA levels and diffuse infiltrates of lymphocytes (**F**). Correlations were examined using Spearman's rank correlation coefficient.

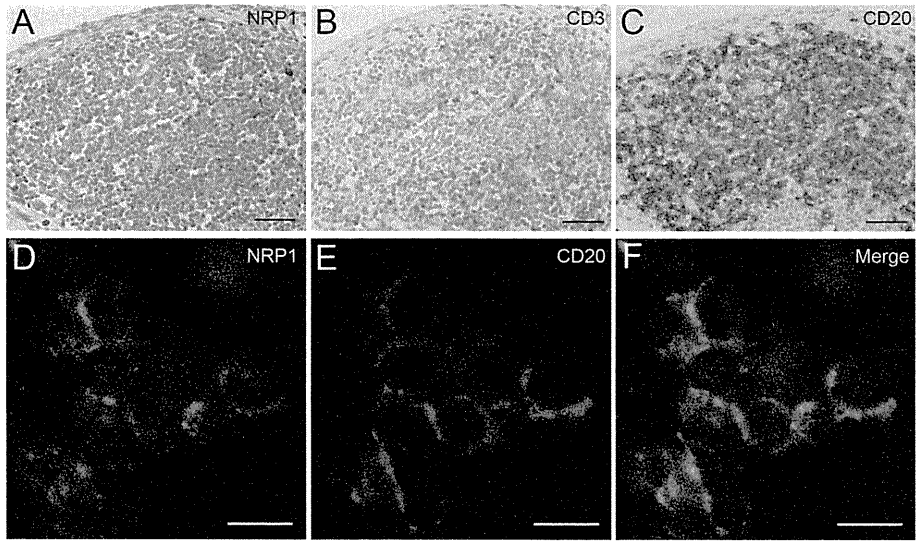

Figure 4 Immunohistochemical and double immunofluorescence staining of lymphocyte aggregates. NRP1 was abundantly expressed by inflammatory cells of lymphocytes aggregates (**A**). Immunohistochemical staining of sequential sections showed that NRP1-positive cells in lymphocytes aggregates also expressed CD3 (**B**) or CD20 (**C**). Micrographs show the double immunofluorescence detection of NRP1 (**D**, green) and CD20 (**E**, red) with the merged images (**F**). The NRP1 positive signal colocalized with the CD20 positive signal in the inflammatory cells of lymphocyte aggregates. A–C, scale bars = 50 μm; D–F, scale bars = 10 μm.

immune responses, and its expression levels are altered in several autoimmune diseases [29,37,38]. The NRP1 and PlexinA complex mediates Sema3A signaling in the immune system [39]. NRP1 is expressed by regulatory T cells, a subset of T cells [40] and PlexinA4 regulates T cell proliferation and activation through inhibition of the actin-cytoskeleton rearrangement and T cell receptor polarization [9]. Recently, it was reported that Sema3A promotes regulatory T cells by enhancing IL-10 production [14]. Regulatory T cells play an important role in maintaining immunological self-tolerance by suppressing autoreactive T cells [41]. Immunohistochemical staining in the current study revealed that Sema3A is expressed in the lining layer. Thus, in OA joints, secreted Sema3A from the lining layer may enhance regulatory T cell functions to suppress autoimmune responses in the sublining layer. In RA, the reduction of Sema3A may abrogate the functions of regulatory T cells, thus allowing the infiltration and focal aggregation of autoreactive lymphocytes in the sublining layer. Further investigation of the correlation between Sema3A and IL-10 expression levels may increase our understanding of their roles in RA.

Catalano reported synovial tissues derived from healthy controls, OA and RA patients exhibited no significant differences although the relative Sema3A expression was lowest in RA samples [14]. This discrepancy might be explained by the difference in sampling numbers, which can influence statistical power, and/or by different qPCR methods used. We quantified *Sema3A* mRNA expression in a larger number of RA patients (n = 30) and OA patients (n = 23), whereas Catalano used relatively small numbers of RA (n = 10), OA (n = 10) patients and healthy controls (n = 5). For qPCR, we used the standard curve method for relative quantification, whereas Catalano used a comparative Ct method.

Sequential immunohistochemical staining revealed that B cells were observed mainly in the lymphoid follicles, consistent with a previous report [36]. Here we observed that B cells in the follicles expressed NRP1 (Figure 4). Vadasz *et al.* recently suggested that Sema3A can modulate the autoimmune properties of B cells in SLE [13]. Thus, Sema3A may exert similar functions in NRP1-positive B cells from RA synovial tissues. Vadasz *et al.* also reported Sema3A serum levels were significantly lower in SLE patients ($p < 0.0001$) and RA patients ($p = 0.047$) compared with healthy controls [13]. Since Sema3A is a secreted soluble protein and can enter the systemic circulation [16,42], lower Sema3A serum levels in RA patients may reflect its reduced expression in knee joints and/or other organs. Additional investigations to quantify the serum levels of Sema3A from OA and RA patients may contribute to further elucidation of pathogenesis of the disease.

It is unclear which factors regulate Sema3A expression in synovial tissues. However, Fukamachi *et al.* reported that the presence of calcium and histamine could modulate Sema3A expression levels in human keratinocytes and fibroblasts [43]. Since histamine is associated with RA pathogenesis [44,45], it may be responsible for the decreased Sema3A levels observed in RA synovial tissues.

We found that mRNA expression of *VEGF-A* was not significantly altered in OA and RA synovial tissues. Hashimoto *et al.* reported staining intensity for VEGF expression did not differ between RA and OA synovial lining [46] and Lowin *et al.* reported that $VEGF_{165}$ expression did not differ in the chronically inflamed tissue of RA patients and OA patients [47]. In contrast, several reports showed altered expression of VEGF in RA. Lee *et al.* observed significantly higher levels of VEGF protein in RA compared with OA synovial fluid and serum [48]. Kurosawa *et al.* observed significant correlations of serum VEGF levels with DAS28-CRP scores [24]. The elevation of VEGF protein in RA synovial fluid and serum may explain the higher total number of VEGF-producing cells in the region [46]. Indeed, our study showed no signification correlation between *VEGF-A* expression levels and DAS28-CRP scores (Figure 2), but there was a marked increase of synovial tissue thickness of the lining layer in RA (Figure 1). Thus, VEGF levels in RA serum may be increased as previously reported [24]. In an earlier study, Ikeda *et al.* reported $VEGF_{165}$ was expressed in 41% of RA samples (17 patients) but not in OA samples (8 patients) using reverse transcription-PCR [49]. They also found *NRP1* was up-regulated in RA synovial tissues. However, we did not observe significant alterations of *VEGF-A* (Figure 2B) or *NRP1* (Figure 2C) between OA and RA specimens. Kim *et al.* reported that NRP1 expression was similar in OA and RA using immunohistochemical analyses [50]. These discrepancies might be explained by the difference in sampling numbers, disease duration of the populations studied, extent of inflammation, use of anti-rheumatoid drugs, and/or by different methods for analysis of NRP1 expression levels. Additional investigations in a large sample considering several different conditions are required to clarify these discrepancies.

Although Sema3A inhibits endothelial formation and angiogenesis due to competition with $VEGF_{165}$ [51], this study did not identify a significant correlation between *Sema3A* mRNA expression levels and blood vessel density in RA synovial tissues. This suggests that angiogenesis in RA lesions may be regulated by other mediators, such as placenta growth factor 1, IL-2 and hepatocyte growth factor [47,52].

The imbalance between Sema3A and VEGF may also affect the etiology of RA. Although *VEGF-A* expression levels did not exhibit a significant correlation with DAS28-CRP scores, the *Sema3A/VEGF-A* mRNA ratios demonstrated a relationship with the RA clinical score. Several studies have demonstrated that anti-NRP1 peptides

suppressed the survival, adhesion and migration of $VEGF_{165}$-induced synovial cells, which contribute to cartilage destruction in RA [50,53]. $VEGF_{165}$ also increased the production of cytokines by human peripheral blood mononuclear cells [54]. Sema3A may inhibit the action of $VEGF_{165}$ on synovial cells and inflammatory cells in a competitive manner.

Innervation is important in the pathogenesis of arthritis. Primary afferent sensory nerve fibers are proinflammatory, whereas sympathetic nerve fibers are anti-inflammatory [55]. In RA synovial tissues, numbers of sympathetic nerve fibers decreased while sensory nerves increased when compared with OA [56]. The loss of sympathetic nerve fibers in RA may be caused by increased Sema3C and its soluble receptor NRP2 [6,55]. However, the mechanism of increased sensory nerve fibers in RA synovial tissues is not fully understood. Decreased Sema3A expression in RA may facilitate the increase of sensory nerves over sympathetic nerves in inflamed RA synovium [55].

Several limitations of our study should be addressed. First, this study population may be influenced by environmental factors as well as genetic factors. Second, patients enrolled in our study were in the advanced stages of RA disease (mean duration 16.3 years). Thus, our data do not reflect the pathogenesis of RA during the early stages. Third, anti-rheumatoid drugs may alter the expression level of Sema3A and other molecules. In this study 12 patients (40%) received methotrexate (MTX) (mean prednisolone daily dose 2.9 mg), 4 patients (13.3%) received TNF-α blockade (3 patients in combination with MTX, 1 patient in combination with sulfasalazine, mean prednisolone daily dose 3.6 mg), 11 patients received Disease Modifying Antirheumatic Drugs (DMARDs) without MTX (mean prednisolone daily dose 1.6 mg), and 3 patients received prednisolone alone (daily dose 6.2 mg). Although there was no statistically significant difference in *Sema3A* expression, DAS28-CRP, or Rooney's inflammation score between the MTX–treated group and other groups (data not shown), we cannot rule out the possibility of altered Sema3A expression by anti-rheumatoid drugs, because each group sample size is small in this study.

Conclusions

This study demonstrated that Sema3A expression levels and the disease activity score in patients with RA negatively correlated with histological parameters in RA synovial tissues. This suggests that Sema3A may have a suppressive effect on the pathological severity of RA. Further elucidation of the role of Sema3A in joints may elucidate the biological and pathological functions of Sema3A and allow the development of new strategies for the treatment of RA.

Additional file

Additional file 1: Expression of $VEGF_{165}$ mRNA in synovial tissues: preliminary study. Expression levels of $VEGF_{165}$ mRNA were measured by real-time PCR. The mRNA levels were normalized to the expression of *β-actin*. The box plots demonstrate the 10th and 90th percentile (whiskers), the 25th and 75th percentile, and the median. $VEGF_{165}$ mRNA levels were not significantly altered in RA (n = 25) synovial tissues compared with OA (n = 17) (A). $VEGF_{165}$ expression levels did not significantly correlate with DAS28-CRP (B).

Abbreviations

DAS28-CRP: 28-joint disease activity score based on c-reactive protein; HE: Hematoxylin and eosin; IL: Interleukin; NRP1: Neuropilin1; NRP2: Neuropilin2; OA: osteoarthritis; qPCR: Quantitative real-time polymerase chain reaction; RA: Rheumatoid arthritis; Sema3A: Semaphorin3A; Sema3C: Semaphorin3C; Sema3F: Semaphorin3F; Sema3G: Semaphorin3G; SD: Standard deviation; SLE: Systemic lupus erythematosus; TNF-α: Tumor necrosis factor-α; $VEGF_{165}$: Vascular endothelial growth factor 165.

Competing interests

The authors declare that they have no competing interests. This work was supported by supported by Grants-in-Aid for Scientific Research nos. 30170517 (to T.S) and nos. 23590429 (to Y.N) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT), and by Grant nos. 07085023 (to Y.G.) from the National Project on Protein Structural and Functional Analyses of MEXT.

Authors' contributions

TS participated in the design of the study, performed the experiments and statistical analysis, drafted and revised the manuscript. NF designed the study, analyzed data, drafted and revised the manuscript critically. KK helped with collection and acquisition of the data and the synovium and revised the manuscript critically. NY assisted in scoring histological parameters and revised the manuscript critically. GY designed the study and revised the manuscript critically. ST helped with collection of the clinical materials and revised the manuscript critically. All authors read and approved the final manuscript for publication.

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Pyoderma Gangrenosum With Wrist Joint Destruction: Case Report

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Pyoderma gangrenosum (PG) is a rare, noninfectious, neurotrophic dermatosis. We observed a case of PG mimicking cutaneous and osteoarticular infections that presented with a prolonged ulcer on the forearm, severe wrist pain, anemia, substantial local and systemic inflammation as evaluated by serum laboratory data, and carpal osteolysis. Although PG rarely damages joints, the ulcer extended to the joint and destroyed the osteochondral tissues. Advanced ulcerative colitis, which is a most common comorbidity of PG, proved to be an underlying disease. Antibiotic and surgical treatment did not heal the ulcer, which was successfully treated with corticosteroids. This intractable ulcer is often misdiagnosed. Hence when a patient presents with an enlarged, painful, unusual skin lesion, PG should always be considered. *(J Hand Surg 2013;38A:357–361. Copyright © 2013 by the American Society for Surgery of the Hand. All rights reserved.)*

Key words Destructive change in wrist joint, noninfectious neutrophic dermatosis, pyoderma gangrenosum, ulcer, ulcerative colitis.

PYODERMA GANGRENOSUM (PG) is a noninfectious necrosis characterized by heavy neutrophil infiltration, engorged veins and capillaries, hemorrhage, and coagulation.[1,2] It typically begins as a pustule or vesiculopustule that progresses to an ulcer with undermined borders. Half of patients have an associated underlying systemic disease such as ulcerative colitis (UC), Crohn disease, rheumatoid arthritis, and other autoimmune diseases.[3,4] Thus, the awareness of the characteristic ulcer is also important for diagnosing the underlying disease.

Pathogenesis is still unknown, but heavy neutrophil infiltration is clearly relevant, and recent studies demonstrated increased expression of the pro-inflammatory cytokines in this disease.[5] Therefore, PG could possibly invade joints, and this has been reported for PAPA syndrome (pyogenic sterile arthritis, PG, and acne),[6–8] which is caused by the mutations of the gene.

We present a case of PG that was previously misdiagnosed as an infectious disease and, therefore, led to a prolonged skin ulcer, advanced UC, and destruction of the wrist joint.

CASE REPORT

The patient was a 60-year-old woman who complained of high fever, diarrhea, and anemia along with pain, swelling, and redness in the left wrist, without any previous history of skin ulcer or arthritis. The pain began with a small papule on the left forearm. The papule progressed to form a small ulcer. She first visited a hospital near her home where necrotizing fasciitis was suspected based on her white blood cell count of 15,600/μL and C-reactive protein level of 22.4 mg/dL. The necrotic tissue in the left forearm was debrided. Tissue samples were submitted for microbiological culture, but the result was negative. Despite these negative results, the antibiotic treatment was continued; nevertheless, a deep ulcer gradually formed on the dorsal forearm. The deep, large skin lesion was treated with

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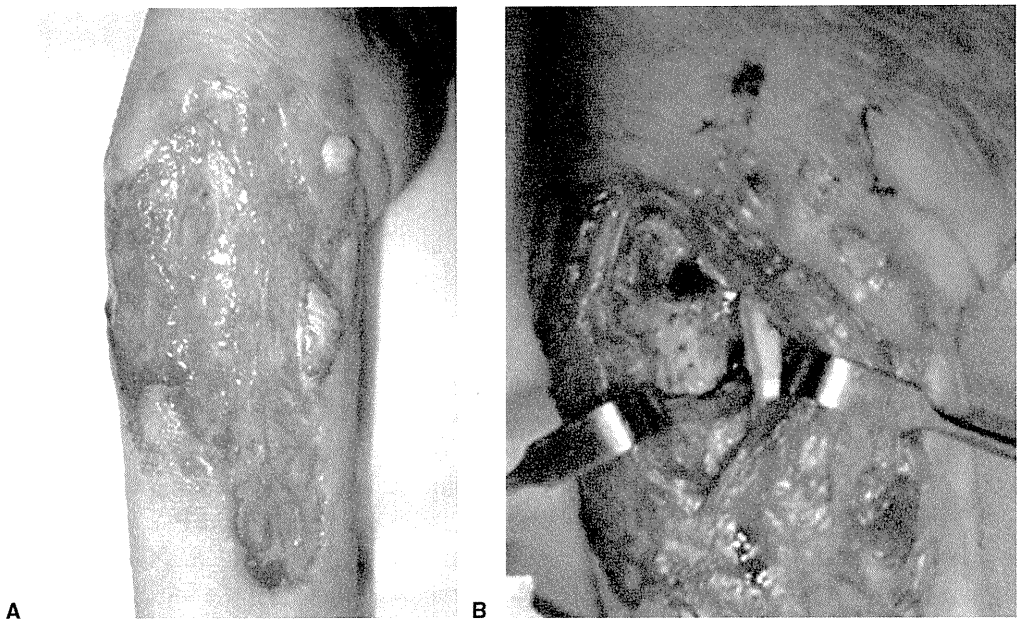

FIGURE 1: Ulcer on the palmar side of the left forearm. **A** Relapsed ulcer on the volar left forearm. **B** The ulcer had a violaceous border and extended into the radiocarpal joint.

dermal grafting, and her wound appeared to be epithelialized 2 months after the surgical procedure. Follow-up was discontinued, although high fever, wrist pain, and diarrhea persisted. In June 2007, she had an ulcer on her volar forearm with increased wrist pain.

On presentation to our hospital, the patient complained of general malaise, diarrhea, and severe pain in her left hand. Her white blood cell count was 11,400/μL, and C-reactive protein level was 10.7 mg/dL. She was severely anemic, and her hemoglobin level was 3.4 g/dL. She was hospitalized immediately. The possibility of rheumatoid arthritis was excluded because laboratory data for rheumatoid factor were normal, and there was no arthritis in any other joint. She experienced persistent pain in the left wrist but not elsewhere. The ulcer had spread volarly with a violaceous border overhanging the ulcer bed (Fig. 1). In contrast to the normal X-ray findings at the previous hospital, current X-rays revealed destructive changes in the radioulnar and radiocarpal joints (Fig. 2A), and magnetic resonance imaging showed inflammation in the radiocarpal joint and in the trapezium (Fig. 2B). On the basis of clinical and radiological findings, we suspected chronic osteoarticular infection and performed surgical debridement. Although results of the microbiological culture were negative, histopathological findings showed infiltration of inflammatory cells into bone and soft tissues (Fig. 3), which is consistent with pyogenic infection, and antibiotics were administered. To identify the cause of anemia and diarrhea, a colonoscopy was also performed, and UC was diagnosed.

Daily administration of 40 mg corticosteroids for UC greatly improved the ulcer on the forearm. A few weeks later, the ulcer showed epithelialization (Fig. 4A), and pain in the wrist had been relieved. However, total colectomy was required to treat advanced UC, and loss of function in the wrist joint was unavoidable (Fig. 4B).

DISCUSSION

In 1908, Brocq reported a series of patients with typical features of the entity named PG in 1930 by Brunsting,[9,10] who believed that a bacterial infection was responsible for this intractable ulcer. The name *pyoderma gangrenosum* has persisted, although PG is currently characterized as noninfectious neurotrophic dermatosis.[11,12] The male/female distribution of PG is equal or with a slight female predominance. The patient's age is generally from 25 to 50 years, although all ages have been reported. [13] Pyoderma gangrenosum usually occurs on the legs, but it can be found anywhere. In 50% of the cases, PG is associated with underlying systemic diseases such as irritable bowel disease, rheumatoid arthritis, and hepatitis,[4,14] but PG has also been reported in healthy individuals.[15] This variant of distributions is one factor of the difficulty of diagnosing PG. Furthermore, PG occurs with minor trauma or surgery in some cases and often mimics a superficial or postoperative infection.[1,16–18]

Powell et al described 4 clinical variants of PG—ulcerative (classic), pustular, bullous, and vegetative.[19] Classic PG starts with sterile pustules or a small papule. The pustules or papules develop into a painful ulcer

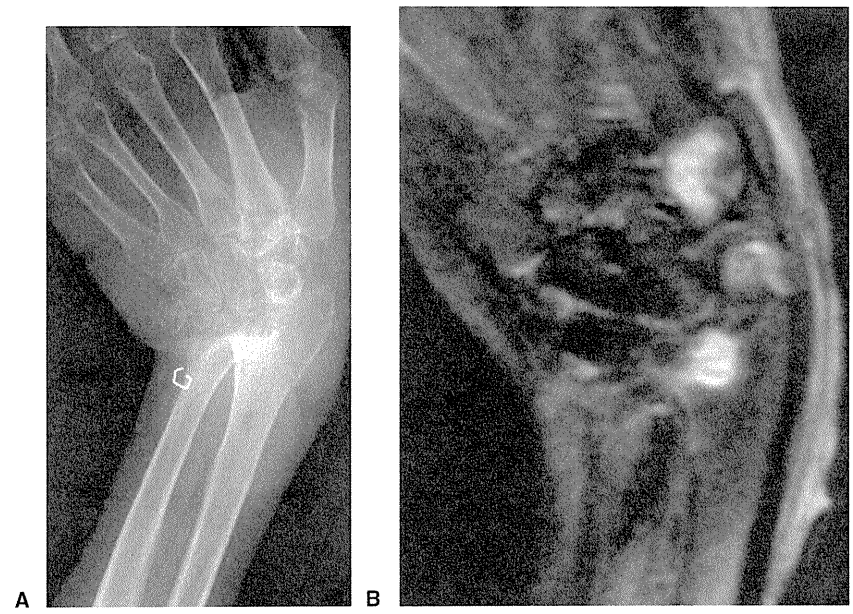

FIGURE 2: Images of the left hand. A X-ray of the wrist joint taken at our hospital shows destructive change in the radiocarpal, ulnocarpal, and midcarpal joints. B Magnetic resonance image of the left hand taken at our hospital shows inflammation in the radiocarpal joint and in the trapezium with high intensity in the T2-weighted image (with fat suppression).

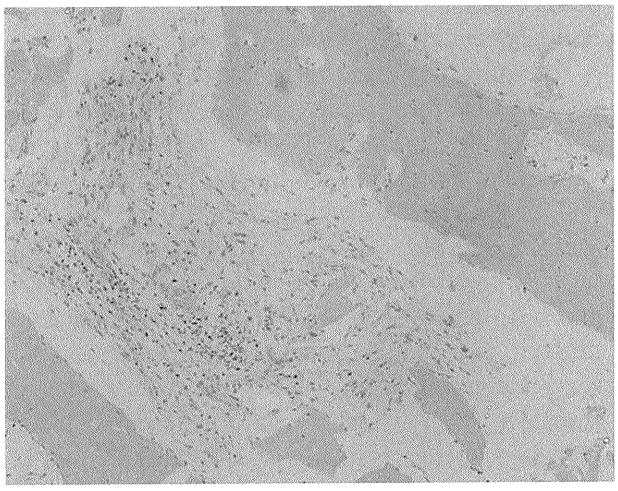

FIGURE 3: Histopathology of the ulcer on the palmar side of the left forearm. Histopathological finding shows infiltration of inflammatory cells including neutrophils (hematoxylin-eosin, original magnification × 100).

with indeterminate, violaceous borders.[2,20] Regardless of the characteristic morphology, diagnostic criteria for PG have not been universally accepted or validated because several variants of ulcer conditions have been observed at several stages.[1,4] Accordingly, diverse appearances and rareness make it especially difficult to definitively diagnose PG.

Diagnosis of PG is based on a history of typical clinical presentation, histopathology, an underling disease, and exclusion of other diseases that would lead to a similar appearance.[1,4,20] Although Su et al proposed diagnostic criteria for PG,[21] to a large extent, the diagnosis of PG is a diagnosis of exclusion.[11] Awareness of the typical features, including association with underlying disease, facilitates making the diagnosis. Careful deliberation and clinicopathologic exclusion of diseases of similar appearance are necessary. In addition, it is essential that PG should be on the list of diagnostic considerations when faced with a patient with unusual skin ulcerations. Therefore, it is important to know the characteristics of PG, which mimics several other diseases and is most commonly mistaken for the infection because of the inflammation and laboratory data.[14]

For differential diagnosis, early papules, nodules, or pustules must be examined for infection, including bacteria, fungal, mycobacterial, and viral, in addition to Sweet syndrome, Behçet sydrome, panniculitides, and cutaneous polyarteritis nodosa. In ulcerative and vegetative lesions, infections, vasculitis, and thrombophilic states, and malignancy must be excluded.[1] Tissue sampling or biopsy must be performed as atraumatically as possible, because it may provoke a pathergy that exacerbates the existing ulcer.

The administration of prednisolone is the most commonly used medication, at a dose of 0.5–2 mg/kg/day, but it should be tapered gradually over 4–6weeks while starting a steroid sparing agent.[11,16,22] Cyclosporine with 3–6 mg/kg/day can be another first-line agent in the treatment of PG.[12] Aggressive surgical debridement

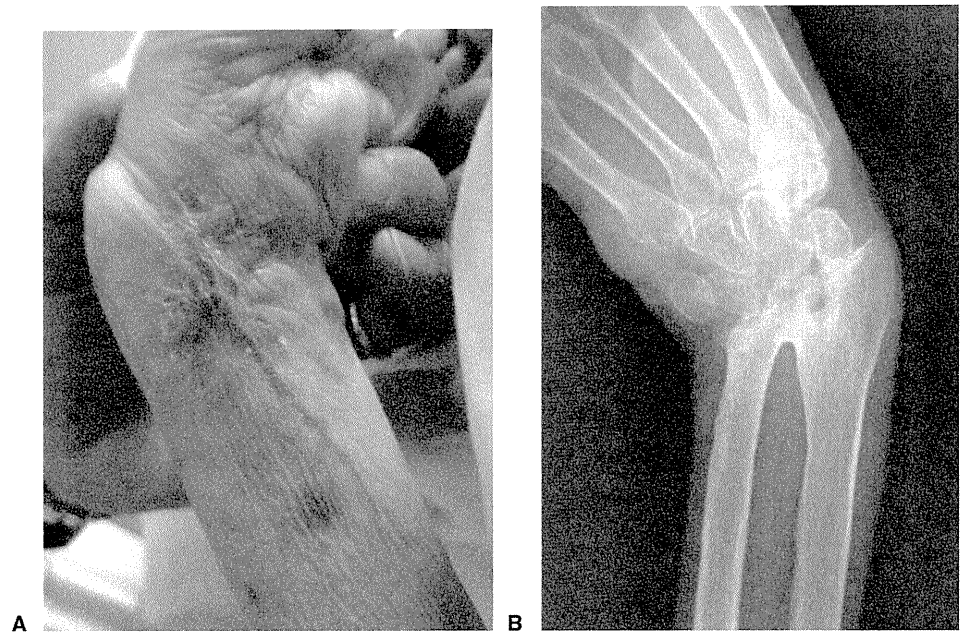

FIGURE 4: Images of the left forearm after administration of corticosteroids A Full epithelialization of the ulcer. B X-ray shows fusion of the distal radioulnar joint and radiocarpal joint.

of the lesion should be avoided because of disease progression secondary to pathergy. Moisture-retentive dressings appear to be suitable for reducing pain, inducing collagen production, facilitating autolytic debridement, and promoting angiogenesis.[2,12] Other multiple systemic and topical treatments (ie, tumor necrosis factor-alpha antagonists and hyperbaric oxygen) have been successfully used for the treatment of PG but are still challenges, because it is difficult to conduct large studies for this uncommon dermatosis.[11,12,20]

Joint deformities are known with PAPA syndrome, [6–8] which typically presents in children with recurrent polyarthritis; PG and acne are caused by the mutations of the gene. Our patient is unique because she had no PAPA syndrome, although her joint was destroyed by PG. Early diagnosis and treatment of PG are favorable to spontaneous healing without complex consequences. Diagnosis and treatment of PG was delayed in our case because the necrotic tissue and destructive changes in the wrist mimicked cutaneous and osteoarticular infection. Accordingly, the chronic ulcer enlarged to the depth of wrist, and PG progressed to joint destruction.

Histopathology is not specific in this disease because pathological findings of PG vary depending on the timing and the site of the biopsy.[2,20] However, lymphocytic or neutrophilic infiltrations are generally shown in an area of ulceration or in an erythematous border[2] and aberrant neutrophil trafficking has been proposed.[23] Furthermore, a recent study demonstrated increased expression of the pro-inflammatory cytokine interleukin-23 in PG patients.[5] Thus, prolonged invasion of inflammatory cells in the skin reached and destroyed osteochondral tissues, and this resulted in the wrist destruction in our case.

The importance and difficulty of diagnosing PG is shown by the present case. Because of the rareness and diverse pathogeneses of PG, the signs and symptoms were misinterpreted. Accordingly, prolonged joint inflammation and advanced UC resulted in a loss of wrist function and necessitated total colectomy. Early diagnosis and proper treatment could likely have hastened and improved the outcome. Surgical treatment and antibiotics were not effective, but corticosteroids were. Pyogenic gangrenosum must be considered when confronted with an enlarged, painful, unusual skin lesion, with or without destructive arthritis that mimics cutaneous and osteoarticular infection.

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Mid- term results of stryker® scorpio plus mobile bearing total knee arthroplasty

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Abstract

Background: The mobile bearing knee system was introduced to lessen contact stress on the articular bearing surface and reduce polyethylene wear. The purpose of the current study was to investigate the mid-term results of patients undergoing total knee arthroplasties (TKAs) using Scorpio Plus Mobile Bearing Knee System (Stryker, Mahwah, NJ), and compare the outcomes between patients with osteoarthritis and osteonecrosis (OA·ON group) and patients with rheumatoid arthritis (RA group).

Methods: Eight males and 58 females were followed up for a period of 4.4- 7.6 years from June 1, 2003 to December 31, 2005. There were 53 knees with osteoarthritis, 17 knees with rheumatoid arthritis, and 6 knees with osteonecrosis. Clinical and radiographic follow- up was done using The Japanese Orthopedic Association knee rating score (JOA score) and Knee Society Total Knee Arthroplasty Roentgenographic Evaluation and Scoring System.

Results: With regard to the JOA score, there was significant improvement in both groups. The postoperative range of motion was between 0.8°and 116.8° in OA·ON group, and between 0.0° and 113.7° in RA group. There were no significant differences with the radiographic evaluation between two groups. Spontaneous dislocation of a polyethylene insert occurred in one patient, and deep infection was occurred in one patient.

Conclusion: There was significant improvement with regard to the clinical and radiographic results of patients undergoing TKAs using the model. The risk of polyethylene insert dislocation related to the mobile bearing TKA is a cause for concern.

Keywords: Total knee arthroplasty, Mobile- bearing design, Osteoarthritis, Rheumatoid arthritis

Introduction

Total knee arthroplasty (TKA) is a safe and effective procedure designed to improve function and relieve the pain associated with osteoarthritis (OA), rheumatoid arthritis (RA), osteonecrosis (ON), and other types of arthritis. The mobile bearing knee system was introduced to lessen contact stress on the articular bearing surface and reduce polyethylene wear. Theoretically, by allowing tibial motion relative to the polyethylene insert, the mobile bearing knee system can improve knee flexibility and kinematics [1].

The Scorpio Plus SuperFlex posterior- stabilized (PS) mobile bearing knee system (Stryker, Mahwah, NJ) has been designed to provide natural rollback, increased implant conformity, and deep flexion. The femoral model has adopted a single antero- posterior and medio- lateral radius design, resulting in joint stability and quadriceps efficiency. A lowered posterior lip of the polyethylene insert lessens excess tension of both tibial and fibular collateral ligament and does not disturb deep flexion (Figure 1A, 1B). The model makes use of a mushroom-shaped post as part of the metal tibial tray which engages with the polyethylene insert and the mechanism allows unlimited internal and external rotation of the insert on the tibial articular surface (Figure 1C- 1E). On the other hand, other types of mobile systems including the low contact stress prosthesis (LCS, DePuy) and

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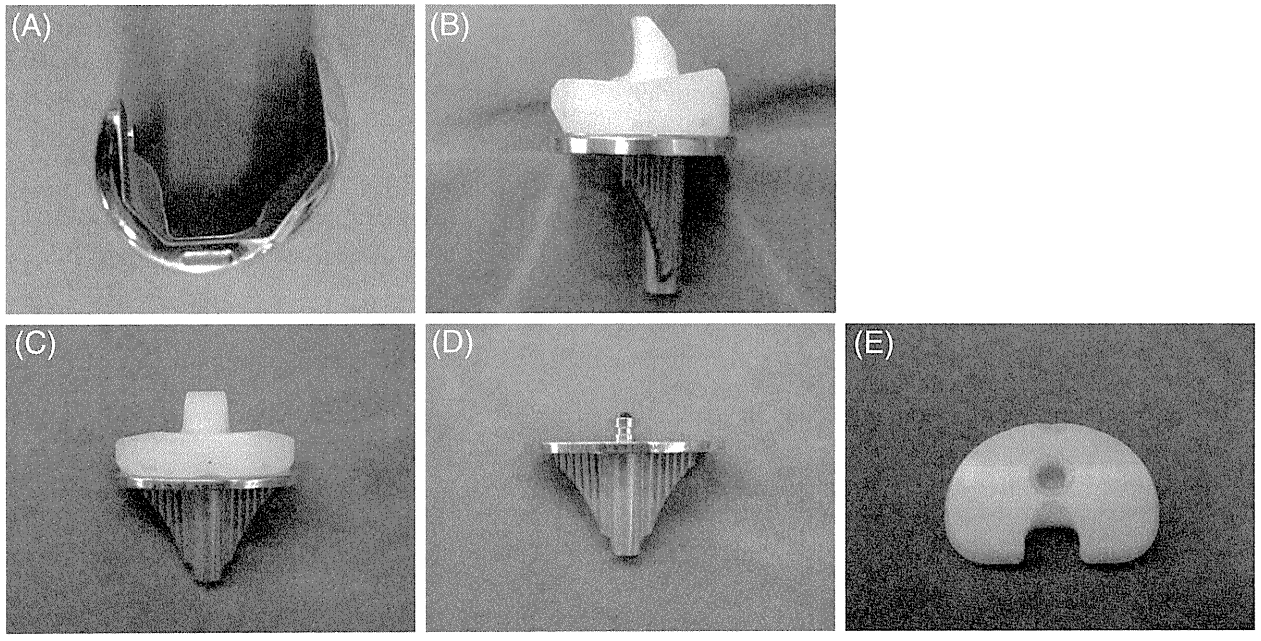

Figure 1 Photographs of the Scorpio Plus SuperFlex posterior- stabilized mobile bearing knee system showing the lateral (A, B) and the anterior (C, D) views and the mobile bearing surface with locking ring (E).

press-fit condylar prosthesis (PFC, DePuy) utilize a central cone as part of the polyethylene insert which engages a matching conical cavity in the tibial tray. Thus, mechanism of rotation is quite different among the various manufacturers of mobile- bearing TKAs. Although many studies have been performed to investigate clinical results of mobile bearing TKAs and similar clinical outcomes have been reported between mobile bearing and fixed bearing TKAs [2,3], the differences of design, shape, and mechanism of rotation might bring different clinical and radiographic results. Over 100,000 TKAs using the Scorpio mobile bearing system have been performed all over the world. However, to the best of our knowledge, no one has reported the clinical and radiographic results of the model. In addition, there are few reports assessing clinical result of mobile bearing TKAs in patients with RA [4]. Medial/ lateral laxiety or anteroposterior instability of patients with RA might result in worse clinical results compared with results of patients with OA. The purpose of the study was to investigate the mid- term results of the Scorpio PS mobile bearing TKA and to compare results between patients with OA and ON (OA·ON group) and patients with rheumatoid arthritis (RA group).

Materials and methods

Patients

113 primary TKA operations on 101 patients were done using Scorpio mobile bearing system between June 2003 and December 2005. Thirty two patients (34 knees) were lost to follow-up and 3 patients (3 knees) had died prior to follow- up investigation. Finally, 76 primary TKA operations on 66 patients were enrolled in this study. This study was approved by the Institutional Review Board, and all patients provided informed consent to participate in it. Fifty-three knees had OA, six knees had ON, and seventeen knees had RA. There were 8 male and 58 female patients ranging in age from 51 to 82 years. Demographic data are given in Table 1. The mean age at the operation and the preoperative femora- tibial angle (FTA) were significant different between two groups.

Table 1 Preoperative clinical data on patient subgroups

	OA·ON group	RA group
Patient No.	49	17
TKA No.	59 OA:53, ON:6	17
Sex (Male/ Female)	7/ 42	1/ 16
Age at time of operation (yr)	72.2±6.1 *	62.8±8.1 *
	51- 82	52- 79
Body height (cm)	149.8±6.9	151.7±6.9
Body weight (kg)	55.8±9.8	57.8±10.9
Body-mass index (kg/m^2)	24.8±3.6	25.1±4.6
Preoperative Flexion angle (°)	120.3±18.7	109.4±24.2
Preoperative Extension angle (°)	−6.6±8.1	−15.3±12.4
Preoperative JOA score	51.6±8.9	44.1±10.9
Preoperative FTA (°)	184.9±7.9 *	177.2±7.2 *
Follow- up duration (yr)	5.8±0.8	6.1±0.9

* = *P*- values less than 0.01 by Mann- Whitney's *U* test.

Surgical technique

A midline or lateral curved surgical incision with a mid-vastus approach was used. After osteophytes were removed, the anterior cruciate ligament and posterior cruciate ligament were sacrificed. The modified gap technique was used to accomplish the accurate soft- tissue balance. Briefly, the distal femoral osteotomy was perpendicular to the mechanical axis and the proximal tibial osteotomy was perpendicular to the tibial axis in the coronal and sagittal plane. After the initial bone cuts, the soft- tissue release was performed. A balancer or spacer block was used to evaluate soft- tissue balances between the distal femur and the proximal tibia or between the posterior femur and the proximal tibia at both 0°extension and 90°flexion. All components were fixed with cement with resurfacing of the patella. Full weight-bearing and range of motion (ROM) exercises were begun from postoperative day 1.

Clinical and radiographic evaluation

Preoperative and postoperative clinical evaluations were performed using the Japanese Orthopaedic Association osteoarthritis or rheumatoid arthritis knee rating score (JOA score) [5]. In the score, pain on walking, pain on ascending and descending the stairs, ROM, and joint swelling were rated for OA and ON patients with maximum scores of 30, 25, 35, and 10 points, respectively. Similarly, pain, ROM, manual muscle testing of quadriceps, ability of walking, and ability of ascending and descending the stairs were rated for RA patients with maximum scores of 40, 12, 20, 20, and 8 points, respectively. ROM was assessed using goniometer measurement. For radiographic evaluation, preoperative and postoperative radiographs of a standing anteroposterior radiograph and a lateral radiograph were utilized to assess FTA, the angle of components [6].

Statistical analysis

Preoperative clinical data, preoperative and postoperative JOA score, ROM, and radiographic parameters were compared between two groups using Mann- Whitney's *U* test. *P*- values less than 0.01 were considered statistically significant.

Results

Clinical results

The median follow- up period was 5.8±0.8 years (range 4.4–7.6 years). With regard to the JOA score, there was significant improvement in both groups; i.e. from 50.7 points to 83.6 points in OA·ON group, and from 44.1 points to 87.1 points in RA group (Figure 2). The postoperative ROM was between 0.8° and 116.8° in OA·ON group, and between 0.0° and 113.7° in RA group. No significant difference was found in the postoperative JOA score and ROM between OA·ON group and RA group (Table 2). Spontaneous dislocation of a polyethylene insert occurred in one patient with ON, and she had undergone operation. Operative findings revealed failure of the locking ring and the original insert was replaced with a thicker insert. Deep infection was occurred in one knee 18 months after surgery. The infection was treated with debridement and antibiotics therapy, and the revision arthroplasty was successfully performed 23 months after surgery.

Radiographic results

There were no significant differences with regard to the radiographic evaluation between two groups (Table 2).

Discussion

Carothers et al. [2] have performed a meta- analysis study of 3506 mobile- bearing TKAs. In relation to 1880 rotating platform mobile- bearing TKAs, survival rates at 15 years (96.4%), increase of the mean Knee Society Score (62.6 points), mean final flexion (116.6°), and polyethylene dislocation (1.0%) have been reported, and they have concluded that the mobile- bearing TKA had demonstrated excellent results. To compare results of a mobile- bearing TKA with those of a fixed- bearing TKA, which have provided durable long term fixation and excellent survival rates, many authors have made a direct comparison on the use of mobile- bearing and fixed- bearing TKAs in the same patients [4,7-11]. Although Price et al. [8] reported that the American Knee Society Score, the Oxford Knee Score, and pain scores for the mobile- bearing TKA were slightly better than those for the fixed- bearing device, most authors have concluded that there were no differences in both clinical and radiographic results between two designs [4,7,9-11]. As well, a meta- analysis studies have suggested no significant differences in clinical or radiological outcomes, such as Knee Society Scores, Hospital for Special Surgery scores, ROM, and radiographic alignment between mobile- bearing and fixed- bearing TKA [12,13].

Mid- term clinical and radiographic results of the model were equivalent to results of other types of mobile- bearing TKAs described in literatures. Although a lowered posterior lip of the polyethylene insert was considered to allow deep flexion, the average postoperative flexion angle of the model was equivalent to those of other types of mobile bearing TKAs [2,9,13]. Postoperative flexion angle is supposed to have a good correlation with preoperative flexion angle. Additionally, it is influenced by a variety of factors, such as implant design and operative techniques. Therefore, it might be difficult to judge how much the model contributed to postoperative flexion angle. As to this model, only biomechanical laboratory study on human cadaveric specimens to

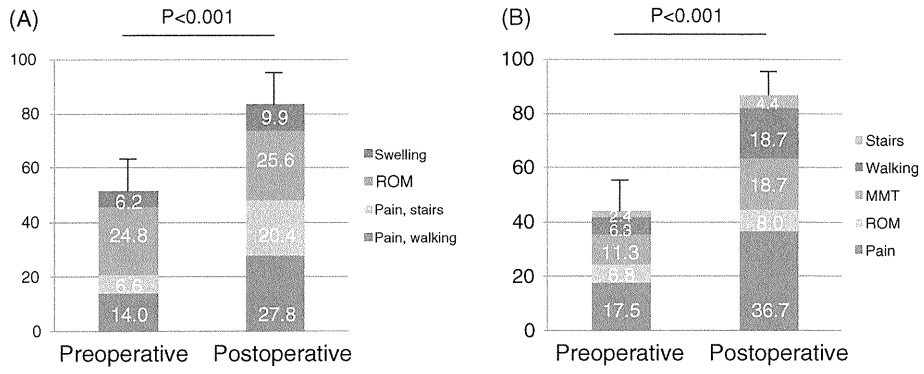

Figure 2 Preoperative and Postoperative JOA score of the OA·ON group (A) and the RA group (B).

assess cortex strain on the anteromedial aspect of the proximal tibia and tibial torsion from axial and rotational loading has suggested that the mobile- bearing prosthesis potentially reduced torque in the proximal tibia during knee rotation compared with the fixed- bearing prosthesis [14].

Dislocation of the polyethylene insert after Scorpio mobile-bearing TKA has been described previously [15]. In general, malpositioned components, flexion-extension gap mismatch, and laxity of soft tissue tension between the femoral and tibial surfaces can cause dislocation of a mobile bearing polyethylene insert [16,17]. In our case, the tension and alignment was considered to be adequate. Our case and duplicated saw bone model demonstrated that failure of the locking system resulted in the dislocation of the insert [15]. Dislocation of polyethylene insert is rare and it can easily be overlooked at the early stage [18,19]. Severe damage to either the femoral or tibial component might occur if there was delay in treatment. When a patient who has undergone TKA complains of pain, swelling, sudden instability, clicking, or locking sensation, it is important to consider insert dislocation as a possible explanation for these symptoms.

Sledge et al. [20] have reported that patients with RA achieve outcomes similar to those of patients with OA with regard to range of motion and pain relief after TKA. Similarly, we found no significant differences between two groups with regard to the clinical results and the radiographic results, although there was significant improvement of the JOA score in both groups. The Norwegian Arthroplasty Register [21] have shown that the cumulative 5- year survival of TKAs was 98.9% in RA patients and 99.3% in OA patients, with revision for infection as the end point. It means that the risk of revision of primary TKAs was statistically higher in RA patients than in OA patients. Therefore, longer follow- up evaluation is necessary to compare results of OA patients and RA patients.

There are some limitations to this study. First, the follow up rate is not adequate for the mid- term results. Although improved follow- up rate might bring different clinical and radiographic results, the number of cases is supposed to be still adequate. Second, there are no control groups in this study. We should have compare results of the design with those of other types of a mobile- bearing TKA.

In conclusion, there was significant improvement with regard to the clinical and radiographic results of the Scorpio mobile- bearing knee model as well as other types of mobile TKA. The risk of polyethylene insert dislocation related to the mobile bearing TKA is a cause for concern.

Table 2 Postoperative clinical and radiographic results of the OA·ON group and the RA group

	OA·ON group	RA group
Postoperative Flexion angle (°)	116.8±16.2	113.7±16.9
Postoperative Extension angle (°)	−0.8±2.5	0.0±0.0
Postoperative JOA score	83.6±12.6	87.1±8.9
α angle	96.7±2.6	96.7±2.0
β angle	88.6±2.5	88.3±2.3
γ angle	6.3±4.1	5.2±4.5
δ angle	86.2±2.7	87.1±2.2
Postoperative FTA (°)	175.6±4.3	175.1±2.6

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
HK, NM, NT, and YA participated in the design of the study. YM, MA, HO, KI, KH, and TI conceived the study, and participated in its design and coordination. HK, NM, YM, NT, YA, MA, HO, KI, KH, and TI performed operation. HK and TS drafted the manuscript. All authors read and approved the final manuscript.

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Good long-term outcome of synovectomy in advanced stages of the rheumatoid elbow

64 elbows followed for 10–23 years

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Background and purpose **Synovectomy is an effective procedure for management of the rheumatoid elbow at radiographically early stages (Larsen grades 1 and 2). However, its efficacy for advanced stages (Larsen grades 3–5) is controversial. We investigated the outcome of synovectomy for advanced stages of the rheumatoid elbow.**

Methods **Between May 1985 and September 1994, synovectomy was performed for 67 rheumatoid elbows in 59 patients (mean age 52 (26–72) years, 54 women). 3 elbows (3 patients) were lost to follow-up after mean 15 (10–23) years. Thus, 64 elbows were evaluated clinically and radiographically.**

Results **The mean Mayo elbow performance score (MEPS) improved from 42 (15–75) points preoperatively to 78 (45–100) points at the final follow-up examination. In cases of Larsen grade 5, the mean MEPS at final follow-up examination (69 points) was lower than those of Larsen grade 3 and 4 cases (80 and 79 points, respectively) ($p < 0.01$). Recurrence of synovitis was obvious in 20/67 elbows. 12 cases had a total elbow arthroplasty mean 13 years after the synovectomy. The 10-year, 15-year, and 20-year survival rates were 97%, 75%, and 70%, respectively.**

Interpretation **Our findings suggest that synovectomy for the rheumatoid elbow gives a good long-term outcome for radiographically judged destroyed joints of Larsen grades 3–4.**

Recently, in addition to conventional disease-modifying antirheumatic drugs, biologic therapies have been widely introduced for the treatment of rheumatoid arthritis (RA). However, despite the existence of these treatments, there are many cases with high disease activity and continuous local synovitis in certain joints.

The elbow joint has high morbidity, followed by joints in the finger, the wrist, the toe, and the knee. The incidence of elbow joint destruction in RA patients is 20–50% (Souter 1990, Mansat 2001). Continuous synovitis may cause progressive joint destruction, which results in severe joint instability or contracture.

The local treatment of continuous synovitis includes physiotherapy and intraarticular injections of steroids. However, when the effects of these treatments are insufficient, surgical treatment is often recommended: synovectomy or total elbow arthroplasty (TEA). Synovectomy is often reported as a successful procedure with relatively few complications for the treatment of rheumatoid elbows at radiographically early stages (Larsen grades 1 and 2) (Stein et al. 1975, Brumfield and Resnick 1985, Saito et al. 1986, Ferlic et al. 1987, Tulp and Winia 1989, Koshino et al. 1991, Gendi et al. 1997, Fuerst et al. 2006). TEA is usually performed for joints at radiographically advanced stages (Larsen grades 3–5) (Figgie et al. 1989, Connor and Morrey 1998, Mansat and Morrey 2000). However, for cases with good ligament stability, we have even performed synovectomies for Larsen grades 3–5, which, however, is controversial (Nestor 1998).

In this study, we investigated the long-term outcome of synovectomy that was performed for the treatment of rheumatoid elbows at radiographically advanced stages.

Patients and methods

From May 1985 to September 1994, we performed synovectomy for 67 rheumatoid elbows at radiographically advanced stages (59 patients, 54 women). 12 elbows were classified as grade 3, 45 as grade 4, and 7 as grade 5 according to Larsen's classification. Mean age at surgery was 53 (26–72) years. 3 elbows in 3 patients were lost to follow-up; thus, data for 64 elbows of 56 patients were used in the study. The 64 elbows

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