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Original Article

Prevalence of and Risk Factors for the Progression of Upper Cervical Lesions in Patients with Rheumatoid Arthritis

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We investigated the prevalence of and risk factors for the progression of upper cervical lesions (UCLs) in patients with rheumatoid arthritis (RA). A retrospective analysis of 49 patients with RA (4 males, 45 females) was conducted. The UCLs included atlanto-axial subluxation and vertical subluxation. We investigated the clinical factors including the Disease Activity Score 28 based on C-reactive protein (DAS28-CRP) and the modified Health Assessment Questionnaire-Disability Index as well as radiographic changes between the baseline (at May 2010 to April 2013) and final follow-up. Forty patients (81.6%) were classified as the non-progressive group, and the other 9 patients (18.4%) comprised the progressive group. The progressive group's final CRP values, baseline or final MMP-3 levels, DAS28-CRP, and rate of pre-existing lesions at baseline were all significantly higher than those of the non-progressive group ($p = 0.017$, $p = 0.043$, $p = 0.002$, $p = 0.008$, $p < 0.001$, and $p = 0.008$ respectively). A multivariate logistic regression analysis demonstrated that DAS28-CRP at baseline was a risk factor for radiographic progression ($p = 0.018$, odds ratio: 2.54, 95% confidence interval: 1.17-5.51). Our findings indicate that higher disease activity might influence the progression of UCLs in patients with RA.

Key words: rheumatoid arthritis, upper cervical spine lesion, risk factor, radiological progression

The cervical spine is commonly involved in patients with rheumatoid arthritis (RA) [1-3]. Deterioration of the cervical spine in RA is a potentially serious disease manifestation that can result in progressive neurological disability caused by mechanical cord compression and cervical spine instability [4, 5]. Cervical involvement is probably a consequence of the intense chronic synovitis that occurs in the joints of RA patients, progressing to bone erosion and ligamentous laxity and finally clinical and radiological instability [6]. This may be progressive with a resultant reduction in life expectancy [7]. It is thus essential to prevent the involvement of cervical lesions in RA, achieving the treat-to-target (T2T) that is based on the European League Against Rheumatism (EULAR) recommendation [8, 9].

Cervical involvement in RA includes three characteristic instabilities: atlanto-axial subluxation (AAS), vertical subluxation (VS), and subaxial subluxation (SAS). Long disease duration and Steinbroker stage III or IV were reported to be risk factors for the presence of cervical lesions [10, 11]. The clinical introduction of biological disease-modifying anti-rheumatic drugs (bDMARDs) has contributed to marked advances in the treatment of RA. bDMARDs have been demonstrated

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to reduce RA disease activity and prevent structural joint damage to small joints such as those in the hand, wrist, and forefoot [12, 13]. Similarly, there is evidence supporting the efficacy of bDMARDs for the treatment of cervical spine lesions, but this remains controversial. Herein we investigated the prevalence of and risk factors for the progression of upper cervical lesions (UCLs) in patients with RA with relatively long disease durations.

Patients and Methods

This retrospective study was approved by the Ethics Committee of our institute (no. 2194). The cases of 49 patients (4 males, 45 females) with RA who had undergone dynamic plain cervical radiography > 2 times were analyzed. Baseline radiographs were taken before orthopedic surgery other than spinal surgery between May 2010 and April 2013. Patients who had a history of prior surgery, prior trauma, or any other symptomatic cervical spine condition were excluded. All patients met both the American Rheumatism Association 1987 revised criteria for RA [14] and 2010 RA classification criteria [15]. The patients' mean age was 59.1 years (range 30-81 years); the mean disease duration was 17.5 years (range 1-46 years), and the mean follow-up period was 38.9 months (range 12-69 months).

According to Steinbroker radiographic grading [16], 13 patients were categorized as stage III and 36 as stage IV. According to Steinbroker functional classification [16], one patient was categorized as class I, 43 patients as class II, and 5 patients as class III. Thirty-one patients (63.2%) were administered prednisolone (PSL) (4.8 ± 2.3 mg/day), and 31 patients (63.2%) were administered methotrexate (MTX) (7.8 ± 2.5 mg/week). The bDMARDs administered at baseline were infliximab in 4 patients, etanercept in 10 patients, adalimumab in 2 patients, tocilizumab in 2 patients, and abatacept in one patient.

Radiographic assessment. Radiographic cervical lesions were defined as follows: an atlanto-dental interval (ADI) of > 3 mm in the form of atlanto-axial subluxation (AAS) [17, 18], and a Ranawat value < 13 mm as vertical subluxation (VS) [19]. Definitions of radiographic progression were an increase in the ADI of > 2 mm for AAS, and/or a decrease in the Ranawat value of > 2 mm for VS [20]. We divided the patients into 2 groups based on the results of their radiographic evaluation at study baseline: the Non-UCL group (n = 16) had no pre-existing upper cervical spine lesions, and the UCL group (n = 33) had AAS and/or VS.

Clinical assessment. The clinical assessment included the patient's disease duration, current medication (prednisolone/MTX/bDMARDs), concentration of C-reactive protein (CRP), rheumatoid factor (RF), Disease Activity Score 28 based on CRP (DAS28-CRP) [21], matrix metalloproteinase-3 (MMP-3) value, and modified Health Assessment Questionnaire-Disability Index (mHAQ) score [22] at baseline and at the patient's final follow-up.

Statistical analysis. The statistical analyses were performed using R for Windows (www.r-project.org). We used Fisher's exact test and the Mann-Whitney *U*-test for the comparisons of the 2 patient groups. *P*-values < 0.05 were considered significant. To assess the risk factors of cervical lesions, we performed a multiple logistic regression analysis. Variables with *p*-values < 0.05 at the baseline in the univariate analysis were analyzed by the stepwise backward selection method.

Results

No significant differences were identified between the Non-UCL (n = 16) and UCL (n = 33) groups in terms of age, gender, interval of radiographic examination, the use of MTX, and the use of PSL. The disease duration and the use of bDMARDs in the UCL group were significantly higher than those in the Non-UCL group ($p = 0.024$ and $p = 0.012$, respectively). The rate of patients who were categorized as Steinbroker stage IV in the UCL group was significantly higher than that in the Non-UCL group ($p = 0.016$) (Table 1). No significant differences were detected between the groups in terms of the baseline or final CRP value, RF, MMP-3 values, DAS28-CRP, final mHAQ score, or the rate of radiological progression. However, the baseline mHAQ score in the UCL group was significantly higher than that in the Non-UCL group ($p = 0.018$) (Table 2).

Based on our definition of radiological progression, we classified 40 patients (81.6%) in the non-progressive group. The other nine patients (18.4%) were classified as the progressive group. No significant differences were observed between the progressive and non-progressive groups in terms of age, gender, disease duration, interval of radiographic examination, use of MTX, PSL, or bDMARDs, baseline CRP values, baseline or

final RF, or mHAQ at baseline and final follow-up. However, the progressive group's final CRP values ($p=0.017$), baseline ($p=0.043$) and final ($p=0.002$) MMP-3 levels, and baseline ($p=0.008$) and final ($p<0.001$) DAS28-CRP and rate of pre-existing lesions ($p=0.008$) at the baseline were all significantly higher than those of the non-progressive group (Table 3).

To compare the relative impact of these variables at baseline, we performed a multiple logistic regression analysis. We analyzed the three variables with p-values <0.05 at the baseline in the univariate analysis (MMP-3 level, DAS28-CRP, and pre-existing spine lesion) by the stepwise backward selection method. The results of the multivariate logistic regression analysis revealed that a higher DAS28-CRP value at baseline was a risk factor for the radiographic progression of UCL ($p=0.018$, odds ratio: 2.54, 95% CI: 1.17-5.51) (Table 4).

Table 1 Patient's background of each group

	Non-UCL n = 16	UCL n = 33	*P* value
Age (years)	60.6 (30–81)	58.5 (32–74)	0.474
Gender (M : F)	1 : 15	3 : 30	1.000
Disease duration (years)	14.3 (1–46)	19.5 (1–46)	0.024*
Follow-up period (month)	38.7 (12–64)	38.4 (12–69)	0.773
MTX, n (%)	10 (62.5%)	21 (63.6%)	1.000
MTX (mg/week)	4.3 (0–12)	5.3 (0–15)	0.656
PSL, n (%)	10 (62.5%)	21 (63.6%)	1.000
PSL (mg/day)	2.9 (0–10)	3.0 (0–10)	0.933
bDMARDs, n (%)	2 (12.5%)	17 (51.5%)	0.012*
Steinbroker stage IV, n (%)	8 (50.0%)	28 (84.8%)	0.016*

All values are expressed as mean (range). *Statistically significant ($p<0.05$)
UCL, upper cervical lesions; MTX, methotrexate; PSL, prednisolone; bDMARDs, biologic disease-modifying antirheumatic drugs; CRP, C-reactive protein; RF, rheumatoid factor; MMP-3, matrix metalloproteinase-3; DAS28, Disease Activity Score 28; mHAQ, modified Health Assessment Questionnaire.

Discussion

Several research groups have examined the progression of cervical lesions in patients with RA. In a study conducted over the course of 6 years, the percentage of 267 RA patients with any cervical instability increased from 47.6% at the beginning of follow-up to 70.4% by the end of the study [23]. In a 3.9-year study, the progression of cervical spine lesions was observed in 42.9% of 91 patients [24]. In a cohort of patients with early RA, cervical spine lesions were observed in 16% of the patients at 9 years. It has also been proposed that the prevalence might decrease in subsequent years when more-intensive treatment strategies, including bDMARDs, are used in the early stage of the disease [25].

In the present study, the percentage of patients with any cervical instability at baseline (65.3% of 49 patients) increased to 69.4% at the final follow-up. Radiographic progression was observed in 9 (18.4%) cases, which was lower than that observed in previous case studies [20,24]. Active and early treatment with DMARDs has been shown to prevent the development of cervical spine lesions due to RA [26]. A few longitudinal studies

Table 2 Patient's clinical parameters of each group

	Non-UCL n = 16	UCL n = 33	*P* value
CRP (baseline, mg/ml)	0.9 (0–2.6)	0.8 (0–4.7)	0.936
CRP (final, mg/ml)	0.3 (0–1.8)	0.3 (0–1.1)	0.526
RF (baseline, mg/dl)	91.2 (5.1–448.9)	101.7 (1.5–474.9)	0.564
RF (final, mg/dl)	86.8 (1.6–332.1)	112.5 (1.5–1,115.5)	0.678
MMP-3 (baseline, ng/ml)	144.4 (17.0–413.2)	164.2 (17.0–669.4)	0.872
MMP-3 (final, ng/ml)	101.2 (28.9–242.5)	137.0 (17.0–465.1)	0.235
DAS28-CRP (baseline)	3.3 (2.0–5.6)	3.2 (1.5–6.3)	0.890
DAS28-CRP (final)	2.2 (1.1–3.8)	2.3 (1.1–3.7)	0.393
mHAQ (baseline)	0.5 (0–1.5)	0.8 (0–1.6)	0.018*
mHAQ (final)	0.6 (0–2.3)	0.8 (0–2.9)	0.189
progression, n (%)	1 (6.3%)	8 (24.2%)	0.238

All values are expressed as mean (range). *Statistically significant ($p<0.05$)
UCL, upper cervical lesions; MTX, methotrexate; PSL, prednisolone; bDMARDs, biologic disease-modifying antirheumatic drugs; CRP, C-reactive protein; RF, rheumatoid factor; MMP-3, matrix metalloproteinase-3; DAS28, Disease Activity Score 28; mHAQ, modified Health Assessment Questionnaire.

Table 3 Univariate analysis comparing the non-progressive and progressive groups

	Non-progressive n = 40	Progressive n = 9	*P* value
Age (years)	58.9 (30–81)	60.3 (32–77)	0.542
Gender (M : F)	4 : 36	0 : 9	1.000
Disease duration (years)	18.5 (1–46)	17.2 (1–29)	0.901
Follow-up period (month)	37.6 (12–69)	42.1 (12–69)	0.688
MTX, n (%)	27 (67.5%)	4 (44.4%)	0.259
MTX (mg/week)	4.9 (0–12)	5.2 (0–15)	0.751
PSL, n (%)	24 (60.0%)	7 (77.8%)	0.454
PSL (mg/day)	2.8 (0–10)	4.0 (0–8)	0.160
bDMARDs, n (%)	17 (42.5%)	2 (22.2%)	0.451
CRP (baseline, mg/ml)	0.7 (0–2.9)	1.4 (0.3–4.7)	0.076
CRP (final, mg/ml)	0.3 (0–1.0)	0.8 (0–2.1)	0.017*
RF (baseline, mg/dl)	91.0 (1.5–474.9)	130.4 (1.5–452.6)	0.923
RF (final, mg/dl)	105.9 (1.5–1,115.5)	96.1 (1.5–393.7)	0.524
MMP-3 (baseline, ng/ml)	146.0 (1.5–669.4)	205.7 (77.9–386.1)	0.043*
MMP-3 (final, ng/ml)	102.5 (17.0–380.7)	235.3 (66.4–465.1)	0.002*
DAS28-CRP (baseline)	3.1 (1.5–5.6)	4.1 (3.0–6.3)	0.008*
DAS28-CRP (final)	2.1 (1.1–3.8)	3.2 (1.1–4.0)	< 0.001*
mHAQ (baseline)	0.7 (0–1.6)	0.9 (0.4–1.4)	0.133
mHAQ (final)	0.7 (0–1.9)	1.2 (0.1–2.9)	0.068
Pre-existing spine lesion (baseline, n (%))	15 (37.4%)	8 (88.8%)	0.008*

All values are expressed as mean (range). *Statistically significant ($p < 0.05$)
MTX, methotrexate; PSL, prednisolone; bDMARDs, biologic disease-modifying antirheumatic drugs; CRP, C-reactive protein; RF, rheumatoid factor; MMP-3, matrix metalloproteinase-3; DAS28, Disease Activity Score 28; mHAQ, modified Health Assessment Questionnaire.

Table 4 Multivariative analysis for predictive factors of the progression of cervical spine lesions

	P value	Odds Ratio	95% CI
DAS28-CRP (baseline)	0.018*	2.54	1.17–5.51

*Statistically significant ($p < 0.05$)
DAS28-CRP, Disease Activity Score 28 on C-reactive protein.

have suggested that DMARDs have an effect on cervical spine instability (CSI), which may lead to reduced prevalence in the future [20, 27]. On the other hand, some authors reported that MTX and biologics had no effect on CSI [11, 28].

Kaito *et al.* reported that the presence of pre-existing cervical spine lesions, high baseline DAS28-CRP values, and final MMP-3 levels were risk factors for the progression of cervical spine lesions [24]. In that study, a higher DAS28-CRP value at baseline was also found to be a risk factor for the progression of UCL. Moreover, all patients with radiographic progression had more than moderate disease activity (MDA: DAS28-CRP > 2.7) at baseline, and 8 of the patients had MDA even at final follow-up. In the patients with UCLs, both the rate of use of bDMARDs and the radiological progression of cervical lesions were higher compared to those of the patients without UCLs. These results suggest that T2T is important to prevent the progression of cervical lesions, regardless of the use of bDMARDs.

Some authors have reported that patients with CSI showed longer RA disease durations, a higher RA stage, and higher mHAQ scores [10, 11]. Our present analyses revealed that all 49 of the patients were Steinbroker stage III or IV. The average disease duration, the rate of Steinbrocker stage IV, and the mHAQ score in our patients with UCLs were significantly higher compared to those of the patients without UCLs. These results suggest that long-term inflammation might cause the development of UCLs as well as peripheral joint destruction. The levels of activities of daily living among RA patients might be decreased by instability of the cervical spine.

A recent meta-analysis showed that female gender, positive RF, long-term corticosteroid treatment, peripheral joint erosion, younger age, long RA duration, and higher disease activity markers were risk factors for CSI in patients with RA [29]. RA patients with

a long disease duration have experienced more severe bone destruction and cervical involvement (especially patients with poor disease control). Patients with a long course of RA are thus considered to have a higher probability of concurrent CSI, due to the characteristic of chronic and persistent disease. For the better treatment of rheumatoid cervical lesions, early aggressive pharmacological intervention before destruction of the ligaments might be required. It would also be useful to detect rheumatoid upper cervical spine synovitis using advanced imaging modalities.

There are several limitations to the present study. First, all patients were diagnosed with CSI, according to the inpatient medical databases. Because baseline radiographs were taken before orthopedic surgery, all patients were Steinbrocker stage III or IV. Therefore, the rate of pre-existing CSI was higher than those in previous studies [11, 23, 24]. Secondly, the ability of plain radiographs to visualize bony erosions, the craniocervical and cervicothoracic junctions, and soft tissue abnormalities such as pannus and spinal cord compression is limited. Because it was designed to shed light on upper cervical lesions, this study lacked an analysis of SAS. The development of SAS is reported to be a more multifactorial process compared to the development of AAS and VS [26]. Thirdly, these disease activity indicators reflected only a certain time point during the study period.

In conclusion, higher DAS28-CRP at baseline was a risk factor for the progression of cervical spine lesions in our present series of RA patients with long-standing disease. Early adequate pharmacological interventions might contribute to a decrease in the number of cervical spine lesions.

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