Quantification of Bone Marrow Edema by Magnetic Resonance Imaging Only Marginally Reflects Clinical Neck Pain Evaluation in Rheumatoid Arthritis and Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** Neck pain is common in rheumatoid arthritis (RA) and ankylosing spondylitis (AS). We investigated the correlation of bone marrow edema (BME) on magnetic resonance imaging (MRI) in RA and AS and its association with clinical complaints of neck pain.

Methods. Cervical spine short-tau inversion recovery-MRI and T1w-MRI of 34 patients with RA and 6 patients with AS complaining about neck pain were obtained. Clinical and laboratory data were available. BME was scored by 2 blinded readers using a modification of a published score, including various cervical sites. Degenerative changes were also quantified.

Results. Patients were predominantly women (82.5%), and mean ± SD age was 57.5 ± 11.8 years, C-reactive protein (CRP) was 0.8 ± 1.3 mg/dl, and pain score was 46.0 ± 17.5. BME was detected in 24/40 patients (60%) involving the atlantoaxial region (21%), vertebral bodies (75%), facet joints (29%), and spinous processes (46%). Degenerative changes were identified in 21/40 patients (52.5%), 13 (62%) of whom also had BME in vertebral bodies. No differences were found between patients with versus without cervical BME for clinical assessments: numeric rating scale pain (median ± interquartile range) 5.5 ± 3.0 vs 6.0 ± 4.0 (p = 0.69), Funktionsfragebogen Hannover 68.2 ± 41.0 vs 42.0 ± 55.5 (p = 0.19), Northwick pain score 44.4 ± 21.8 vs 47.2 ± 27.0 (p = 0.83), or CRP 0.40 ± 0.80 vs 0.60 ± 0.66 (p = 0.94). For patients with degenerative changes, symptom duration was longer than for patients without (10 ± 12.5 vs 5.0 ± 18.0 yrs, p = 0.73).

Conclusion. In this small study of patients with RA and AS complaining about neck pain, BME was found in many different cervical sites, including the facet joints and the spinous processes. However, the occurrence and severity of BME did not correlate with the severity of neck pain. (First Release October 15 2016; J Rheumatol 2016;43:2131–5; doi:10.3899/jrheum.150553)

Key Indexing Terms:
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Involvement of the cervical spine is common in both rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Despite differences in their pathogenesis, chronic neck pain is a frequent symptom in both diseases[1]. In RA, neck pain in the cervical spine has been reported in as many as 20% of patients, especially those with long disease duration[2]. These patients may also have degenerative changes similar to patients of this age group who do not have an inflammatory rheumatic disease[3].

Typical magnetic resonance imaging (MRI) findings in the cervical spine of patients with RA and AS include inflammatory changes of the bone marrow that appear as bone marrow edema (BME). However, inflammation may also occur within synovium adjacent to the dens, leading in some cases to laxity of the transverse ligament, and atlantoaxial or subaxial subluxation with resultant myelopathy in severe cases[4]. It remains uncertain how these findings correlate with

neck pain in RA, a symptom that is frequently found independent of major changes in the cervical spine such as subluxation[5] or instability[2,6]. Although there have been major advances in imaging in the last decade, the cervical spine remains a poorly studied region despite the fact that neck pain contributes significantly to patient morbidity in these diseases. In a publication[7,8], an MRI score for quantification of BME, synovitis, and erosions in the cervical spine was proposed, showing that RA disease activity scores are not able to identify activity in the cervical spine region and that MRI may provide useful information regarding inflammation and damage in those patients, alerting clinicians to the presence of significant pathology and influence management.

The aim of our present study was to prospectively evaluate the clinical complaints and the occurrence of BME by MRI in patients with RA and AS and to validate the proposed scoring system in patients who presented with neck pain during routine clinical visits in a tertiary hospital or cooperating rheumatology practices.

MATERIALS AND METHODS

The study was approved by the ethics committee of the University of Muenster, Germany (study number: AZ 2008-204-f-S). All patients gave written informed consent for participation in the clinical part of the study and some of them also agreed to participate in the imaging part, which was analyzed and presented here. Overall, 40 patients (34 with RA diagnosed by the American College of Rheumatology criteria[9] and 6 with AS[10] diagnosed by the modified New York criteria) were included in our prospective study. The baseline demographics of the patients and their MRI scores are presented in Table 1. All patients had participated in the CASSANDRA (Cervical ArthritiS Scoring AND Treatment in Rheumatoid Arthritis) trial[1], in which we analyzed the prevalence, degree, and clinical significance of neck pain in patients with RA and AS who presented to the outpatient clinic of our specialized center for rheumatic diseases or to private rheumatology practices. Presence of clinically relevant neck pain was defined as pain in the neck with an intensity higher than 30 mm on a 0–100 mm numeric rating scale (NRS), and when the neck pain had occurred for more than 2 weeks and with a duration for more than a half day every day. Clinical information about patients' demographics, diagnosis of RA or AS, duration since diagnosis, and disease activity by the 28-joint Disease Activity Score (DAS28)[11] or the Bath Ankylosing Spondylitis Disease Activity Index[12] were recorded. Further, laboratory [C-reactive protein (CRP) and erythrocyte sedimentation rate] as well as the following clinical data were obtained from all patients: Northwick pain score, 0-10 NRS for neck pain, a validated and commonly used test for physical function in the German language [Funktionsfragebogen Hannover (FFbH)[13]], and the occurrence of neurological symptoms (defined as any paresthesia in the arm or fingers).

Table 1. Baseline characteristics of the patients included in this study. Values are mean ± SD unless otherwise specified.

Clinical Feature	All, n = 40	RA, n = 34	AS, n = 6
Age, yrs	57.5 ± 11.8	58.4 ± 10.3	52.2 ± 18.7
Disease-specific symptom duration, yrs	14.4 ± 12.4	13.2 ± 11.2	21.2 ± 17.3
Female, %	82.5	88.2	50
Duration of neck pain, mos	10.6 ± 8.8	10.3 ± 8.5	11.8 ± 11.1
NRS neck pain	5.8 ± 2.0	5.7 ± 2.0	5.8 ± 2.6
CRP, mg/dl	0.8 ± 1.3	0.9 ± 1.4	0.7 ± 0.5
MRI score for BME	2.8 ± 3.6	2.8 ± 3.7	3.0 ± 3.3

RA: rheumatoid arthritis; AS: ankylosing spondylitis; NRS: numeric rating scale; CPR: C-reactive protein; MRI: magnetic resonance imaging; BME: bone marrow edema.

All images were acquired between December 2007 and March 2009 with the same imaging protocol. Inclusion criteria were the clinical diagnosis of RA or AS and the presence of neck pain. MRI investigations were executed with a 1.5 Tesla MRI machine using a phased-array neck coil. The sagittal view was used with the following sequences:

(1) T1-weighted spin-echo sequences [repetition time (TR)/echo time (TE) 500/10-14 ms, slice thickness 3 mm].

(2) Fat-saturated short-tau inversion recovery sequences (TR/inversion time/TE 4000/150/60 ms, slice thickness 3 mm).

Two experienced readers (XB, FH) who were blinded for clinical data and also for the reading results of the other readers evaluated all MR images. A modification of a published MRI scoring system[14] was used as a basis and the observations were quantified by concentrating on the extension of BME in the dens axis as well as in the corpus, facet joints, and spinous process of C2–C7: the dens axis was scored for BME with a scoring of 0 (no BME), 1 (BME in < 1/3 of the bone surface), and 2 (BME in ≥ 1/3 of the bone surface). The vertebral bodies of C2–C7 were scored as follows: 0 (BME < 10% of the bone surface), 1 (10%–33% of the bone surface), 2 (34%–66% of the bone surface), and 3 (> 66% of the bone surface). The same grading of 0–3 was used for the spinous process and for the facet joints, with the right and the left facet joint of C2–C7 being scored together. Thus, the total score ranged between 0–57 points.

In addition, presence or absence of degenerative changes was recorded. Degeneration was defined as loss of intervertebral disc height and water content and/or evidence of disc herniation, chondrosis, or spondylosis.

Statistical analysis. For reliability analysis of the scores between raters, intraclass correlation coefficients and Cronbach's alpha coefficient were calculated based on the total scores. The Mann-Whitney U test was used to compare the data between subgroups at single timepoints, including medians and interquartile ranges (IQR) where appropriate. For analysis, the mean scores of both blinded readers were calculated. In case of disagreement of > 2 scoring points, a senior reader (JB) decided on the final score. Spearman correlation coefficient was used to assess correlations between imaging data and clinical or laboratory variables. Binary variables for occurrence of imaging lesions or positive/negative clinical or laboratory findings were compared using the Fisher's exact test for proportions. A p value of < 0.05 was considered statistically significant. Calculations and statistical analysis were performed using SPSS v23.0.

RESULTS

Reliability and feasibility of the modified scoring system. The correlation between readers was very good, with minor disagreement in the scores of 46/240 vertebrae (19.6%) while major disagreement was seen in the scoring of only 9/240 vertebrae (3.8%). The ICC was 0.89 (95% CI 0.80–0.94) and Cronbach's alpha coefficient was 0.941 (95% CI 0.89–0.97). The mean time required to score the cervical spine of 1 patient was 43 ± 12 s.

Description of pathologic MRI lesions. BME was detected in 24/40 patients (60%, 21 with RA and 3 with AS). Overall, 5 patients (20.8%) had atlantoaxial BME, while 18/24 had BME in a vertebral body (75%), 7/24 (29.2%) in the facet joints, and 11/24 (45.8%) in the spinous process (Figure 1A–D).

Degenerative changes were seen in 21/40 patients (52.5%; Figure 1E), 13 (62%) of whom also had BME in a vertebral body. This contrasted to findings in 19 patients where degenerative changes were not seen, in whom only 5 (26.3%) had

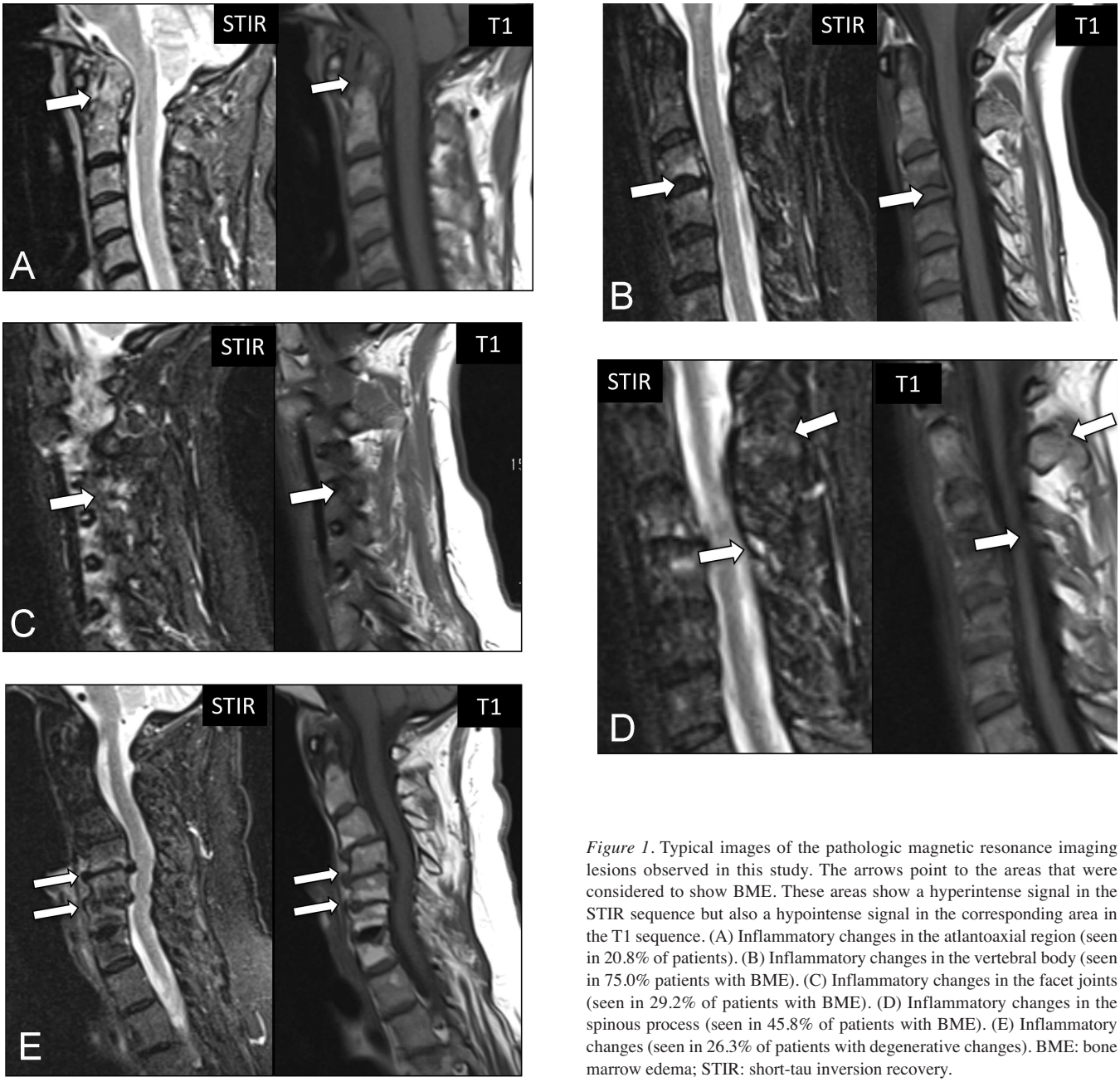

Figure 1. Typical images of the pathologic magnetic resonance imaging lesions observed in this study. The arrows point to the areas that were considered to show BME. These areas show a hyperintense signal in the STIR sequence but also a hypointense signal in the corresponding area in the T1 sequence. (A) Inflammatory changes in the atlantoaxial region (seen in 20.8% of patients). (B) Inflammatory changes in the vertebral body (seen in 75.0% patients with BME). (C) Inflammatory changes in the facet joints (seen in 29.2% of patients with BME). (D) Inflammatory changes in the spinous process (seen in 45.8% of patients with BME). (E) Inflammatory changes (seen in 26.3% of patients with degenerative changes). BME: bone marrow edema; STIR: short-tau inversion recovery.

BME in a vertebral body. For the 52.5% of patients with degenerative changes, the symptom duration in years was longer than for patients without (10 ± 12.5 vs 5.0 ± 18.0, p = 0.73).

In a more detailed analysis of 240 evaluated vertebral bodies, neither BME nor degenerative changes were detected in the majority (178/240, 74.2%) of the evaluated vertebral bodies. Of the remainder, 27/240 (11.3%) of vertebrae showed degenerative changes, and in parallel, BME in the vertebral body. Degeneration only was seen in 24/240 (10%) vertebral bodies, while 11/240 (4.6%) vertebral bodies had BME without degeneration.

Comparison of clinical symptoms and different pathologic MRI lesions. When MRI findings were compared with clinical features, we found no differences between patients with versus without cervical BME lesions for all assessments: NRS pain (median ± IQR) 5.5 ± 3.0 vs 6.0 ± 4.0 (p = 0.69), FFbH 68.2 ± 41.0 vs 42.0 ± 55.5 (p = 0.19), Northwick pain score 44.4 ± 21.8 vs 47.2 ± 27.0 (p = 0.83), DAS28 4.4 ± 2.3 vs 4.2 ± 3.3 (p = 0.33) or CRP 0.40 ± 0.80 vs 0.60 ± 0.66 (p = 0.94).

A correlation between the raw neck pain (NRS) and BME score was not found, independent of whether the degenerative changes were counted as positive (correlation 0.07, p = 0.70)

or were left out of the analysis (correlation 0.15, p = 0.39). There was no correlation between neck pain and the BME score if the atlantoaxial region was not included (correlation 0.01, p = 0.94).

Out of 6 patients who did not show inflammatory activity for neck pain, 2 (33.3%) were taking nonsteroidal antiinflammatory drugs (NSAID) because of clinical neck pain complaints, while 19 out of 29 patients (65.5%) with inflammatory activity for neck pain were taking NSAID (p = 0.19, OR 3.8, 95% CI 0.59–24.5).

Two out of 8 patients without (25.0%) and 10 out of 27 with (37.0%) nondegenerative MRI findings in the cervical spine had neurological symptoms (p = 0.69, OR 1.8, 95% CI 0.30–10.4). None of the 7 patients without (0.0%) and 12 out of 28 with (42.9%) degenerative spinal changes had neurological symptoms (p = 0.070, OR not computable).

DISCUSSION

Our small prospective study examines the relationship between pathologic spinal changes as detected by MRI and the subjective assessments of neck pain in patients with RA and some with AS. Overall, we found that MRI BME was common in patients who complained of neck pain, and this finding was common not only in the vertebral body (75% of patients), but also in the spinous process (46%) and in the facet joints (29%). Degenerative changes of the cervical vertebral bodies were also common, being detected in > 50% of the patients and in 2/3 of these cases they were associated with BME.

We used 2 different approaches to evaluate pathologic MRI findings. The first was to document the presence or absence of different MRI lesions such as inflammatory or degenerative changes in each single vertebra and at different vertebral sites. Although this approach is more practical and relevant for clinical practice, its limitation is that identification of BME thought to be related to rheumatic conditions might be difficult because of the similarity of these changes to other conditions such as osteoarthritis or mechanical stress, but also because of the complicated anatomy in this part of the axial skeleton[14]. The second approach was the quantification of inflammatory changes by using a modification of a proposed scoring system[14]. The main reason for using a modification was that as a part of a clinical protocol for performance of MRI for neck pain, T1-post gadolinium images, which would be necessary for the assessment of synovitis as proposed in the original scoring system, were not approved by the local ethics committee prior to our study. For its application, the used modification showed an excellent interreader reliability and a very good feasibility.

On a per-vertebra analysis, most of the pathologically affected vertebrae showed both inflammation and degeneration. However, the presence of MRI BME showed no association to clinical findings, such as pain (NRS), Northwick pain score, or FFbH, or objective measurements of inflammation such as CRP. Further, the occurrence of cervical BME showed only a trend toward but no good relation with more NSAID use (OR 3.8, 95% CI 0.59–24.5, p = 0.19). This finding is in line with a previous study[14], in which BME was found to be common in the atlantoaxial and the subaxial region, and did not correlate with symptoms of neck pain in the 30 patients with RA (15 with and 15 without neck pain).

There was no association between cervical spine involvement as seen on MRI and the standardized disease activity indices (DAS28, Northwick Park Score) for disease activity or for the occurrence of clinically relevant neurologic symptoms in our study. While the former is a known finding[14], the latter is in contrast to data from the study of Narváez, *et al*[15], where identification of atlantoaxial involvement (stenosis) was strongly correlated with pathologic MRI findings in patients with RA who were symptomatic for cervical spine complaints. Atlantoaxial involvement was defined as spinal canal stenosis with evidence of upper cervical cord or brainstem compression and subaxial myelopathy changes in that study. Such findings were not observed in our patients.

Our study had some limitations. These MRI data are based on the quantification of BME only and did not include evaluation of synovitis. The reason for this was the limitation from the ethics committee to use T1-post gadolinium MRI in our present study. Further, regarding the assessment of inflammatory activity, the definition of BME in the score used herein included a score of "0" for quantification of lesions in the dens axis, but the definition of a score of "0" in the vertebral bodies was defined by a lower cutoff of < 10% of the vertebral area, which could result in some low-level evidence of BME that was not considered positive in these cases. Another limitation is that our study combined data from a small number of patients with AS with a larger number of patients with RA. In addition, no radiographic data of the patients included here could be provided. As mentioned earlier, the protocol of the clinical part of this study (CASSANDRA[1]) was designed to include patients with the clinical symptoms of neck pain. Imaging of these patients was done prospectively, but was not necessary for inclusion in the main (clinical) study. Those who agreed to imaging did this mostly for performance of MRI, while the numbers of those who had both MRI and conventional radiographs available were too few to draw any comparisons. Further, our study was performed with standard MR images as requested in daily clinical practice. We do not know whether MR imaging in flexion views, which has been shown to be useful in evaluating changes in the subarachnoid space in patients with RA[16], would show an even more prominent contribution of this cervical segment for explanation of the reported symptoms of neck pain. Future studies examining similar questions on larger, more homogeneous groups with the same diagnoses and also ideally including a control group with no

chronic inflammatory disease to compare for other reasons of BME will be useful for clarification of possible differences between diagnoses. In a study comparing MRI examinations of the entire spine in patients with possible spondyloarthritis (SpA) and degenerative arthritis[17], MRI lesions considered to be characteristic of SpA could also be found frequently in patients with other noninflammatory diseases. Finally, it also needs to be stressed that our results are based on observations from patients who already had a diagnosis of a chronic inflammatory disease, but were not being compared with a control group of patients symptomatic to neck pain but without such a rheumatologic diagnosis. Such a comparison would have indeed increased the validity of the results of our present study. Nevertheless, a control group was not included in the initial study design because our question to be answered by this examination was derived from the clinical observation of an apparent high prevalence of neck pain in the patients that we see in our daily rheumatology practice.

Taken together, in our dataset of a small substudy of a larger clinical dataset, we found that although MRI BME is common in patients with RA and AS experiencing neck pain, this prevalence may be seen at different sites. On the other hand, many patients still might not show BME on MRI examinations of a single timepoint. A modification of a published scoring system for BME assessment in patients with chronic inflammatory rheumatic diseases was found to be reliable and feasible.

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