Ankylosis of the wrist bones in patients with rheumatoid arthritis: a study with extremity-dedicated MRI

F. Barbieri[1], G. Zampogna[1], D. Camellino[1], F. Paparo[2], M. Cutolo[1], G. Garlaschi[3], M.A. Cimmino[1]

[1]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova; [2]Division of Radiology, Ospedale Galliera, Genova; [3]Division of Radiology, University of Genova, Genova, Italy.

Abstract

Objective

Ankylosis, or spontaneous bone fusion, of the small joints of the hand is a rare event in patients with rheumatoid arthritis (RA), being observed in 0.8% of them on conventional radiographs. It is associated with long-lasting and severe disease. In other settings, such as fracture healing, bone fusion is a reparative process.

The aim of this paper is the study of the frequency of wrist ankylosis in patients with RA in comparison with other arthritides; to correlate ankylosis with disease activity.

Methods

A total of 94 patients affected by RA, 71 patients with different rheumatic conditions and 42 controls with no joint disease or with slight hand osteoarthritis were studied. DAS-28 CRP was calculated in patients with RA and psoriatic arthritis. MRI of the clinically most involved wrist was performed with a 0.2 T, extremity-dedicated MRI system.

Results

Of RA patients, 10/94 (10.6%) showed ankylosis in comparison with 2/113 (1.8%) controls (p=0.015). RA patients with ankylosis had longer disease duration (p=0.019) but similar disease activity.

Conclusion

MRI-defined bone ankylosis is frequent in RA. It is not limited to seronegative spondyloarthritides and may be part of the bone damage observed in RA.

Key words

rheumatoid arthritis, MRI, bone, ankylosis, wrist

Francesca Barbieri, BS, PhD
Giuseppe Zampogna, MD
Dario Camellino, MD
Francesco Paparo, MD
Maurizio Cutolo, MD
Giacomo Garlaschi, MD
Marco A Cimmino, MD

Please address correspondence to:
Dr Marco A. Cimmino,
Clinica Reumatologica,
Dipartimento di Medicina
Interna e Specialità Mediche,
Viale Benedetto XV, 6,
16132 Genova, Italy.
E-mail: cimmino@unige.it

Received on March 5, 2015; accepted in revised form on June 23, 2015.

Funding: this study was supported in part by a grant of the University of Genova (Fondi di Ateneo 2010-2013).
Competing interests: none declared.

Introduction

Ankylosis, or spontaneous bone fusion, of the small joints of the hand is a rare event in patients with rheumatoid arthritis (RA), being observed in 0.8% of them with conventional radiography (1). Among arthritides, RA is considered the disease prototypical of joint destruction, for synovitis and bone marrow inflammation directly lead to joint erosions, with scarce sign of repair (2). Structural damage in RA is predicted by severity and duration of inflammation (3), as well as IgM rheumatoid factor raised levels, anti-citrullinated protein antibodies, and the shared HLA-DRB1 epitope (4). Enzymatic activity, such as that of aggrecanases and matrix metalloproteinases, differentiation of osteoclasts, and inhibition of osteoblast activity and Wnt signalling, conjure to degrade articular cartilage and bone.

Seronegative spondyloarthritides, such as ankylosing spondilytis (AS) and psoriatic arthritis (PsA), are additional erosive diseases that can lead to the resorption of cortical bone, but can also promote the formation of bony spurs at the insertion sites of the entheses. Ossification and ankylosis are the hallmarks of AS, where disease bone remodelling and new cartilage and bone formation occur together with inflammation. However, new insights into the molecules involved in ankylosis, such as bone morphogenetic proteins and Wnts, have suggested that the classical paradigm linking inflammation to ankylosis is doubtful in consideration of the fact that bone formation tends to occur in areas of healed inflammation. One explanation is that during active inflammation TNF-α suppresses new bone formation via Dickkopf-1, a regulator of joint remodelling (5). The concept of uncoupling between inflammation and new bone formation is supported by a mouse model of spondyloarthritis, in which no effect of etanercept, a TNF-α receptor antagonist, on the incidence and severity of joint ankylosis was observed (6).

The occasional finding of RA ankylosis on radiograms has been associated with a disease of long-lasting, severe course, suggesting that the increasing efficacy of RA treatment strategies may lead to its disappearance in the future (1). Nonetheless, we have recently described a patient in whom wrist bone fusion, seen on sequential MRI examinations, was observed after successful control of the disease by biological treatment (7). One possible explanation is that when RA activity is high, synovitis erodes cartilage and bone, with a resulting increase in the joint space. In this setting, bone ankylosis is unlikely. On the contrary, bone fusion is usually a reparative process, for instance in fracture healing (8), or after surgery (9). When inflammation subsides and local synovitis disappears, repair can result in a fused joint, an event that is usually associated with pain cessation. These considerations indicate the possibility that ankylosis could be unrelated to inflammation levels not only in AS but also in RA.

To test the hypothesis that wrist joint ankylosis in RA is related to low disease activity we have reviewed the MRI examinations of a cohort of RA patients, in relationship with their disease activity. An additional endpoint was to compare the occurrence of ankylosis in RA with that observed in patients with other arthritides or in normal controls.

Patients and methods

A total of 94 patients with RA, diagnosed according to the 1987 ACR criteria (10), were studied. The protocol had been approved by the relevant ethics committee and the patients gave their informed consent to review their MR images and clinical charts. There were 27 men and 67 women. Mean age was 54.2±16.1 years. The control group was composed of 22 patients with PsA (14 women, mean age 52.6±14.2), diagnosed according to the CASPAR criteria (11), 13 with connective tissue diseases (12 women, mean age 57.6±16.2 years), 18 with gout (3 women, mean age 65.9±15.7 years), diagnosed according to the preliminary ACR criteria (12), 18 with polymyalgia rheumatica (11 women, mean age 74.7±8.4 years), diagnosed according to the Bird *et al.* criteria (13), and 42 controls (31 women, mean age 50.9±19.8 years), who had no joint disease or had mild hand osteoarthritis. All RA and PsA patients had present or past clinical involvement

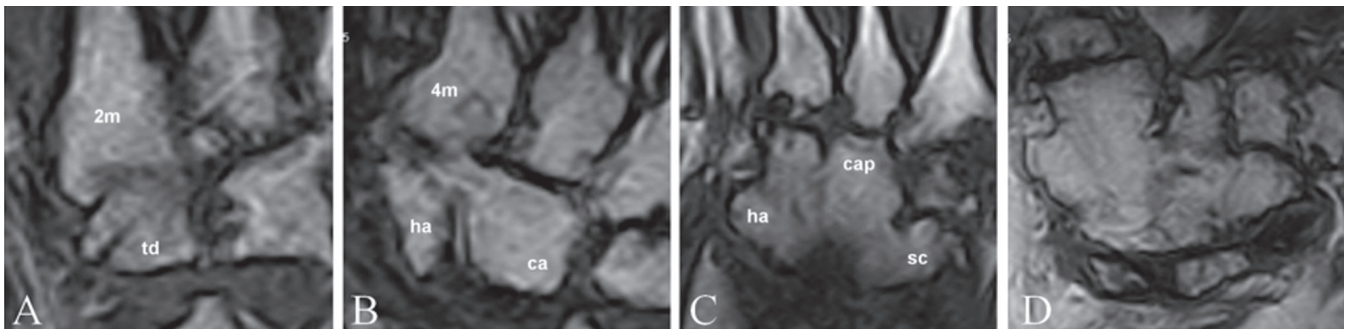

Fig. 1. Examples of bone ankylosis in patients with rheumatoid arthritis between trapezoid (td) and 2nd metacarpal basis (2m) (**a**); between hamate (ha), capitate (ca) and 4th metacarpal basis (4m) (**b**); between ha, ca and scaphoid (sc) (**c**); and complete carpal fusion (**d**).

of the examined wrist, as much as most, but not all, patients with gout or connective tissue diseases. In RA and PsA patients, disease duration, number of tender and swollen joints, general health measured on a 100 mm visual analogue scale, ESR, CRP, and IgM rheumatoid factor (IgM RF) were assessed. DAS-28 CRP was also calculated (14).

MRI of the clinically most involved wrist was performed with a 0.2 T, extremity-dedicated MRI system (Artoscan C, Esaote, Genova, Italy). Areas studied included the bases of the five metacarpals, the wrist bones, radius and ulna (15). The used sequence was a T1 weighed Turbo 3D (TR/TE/NEX 35/16/1 with slice thickness 0.6-0.9 mm) recorded on the coronal plane with subsequent reconstruction in the remaining planes. Ankylosis was defined as partial or total replacement of the joint space between two or more wrist bones by newly formed bone.

One-way ANOVA, Kruskall Wallis test, and chi square test were used as statistical methods. Correlations were evaluated with the Spearman's correlation coefficient. All statistical calculations were performed with MedCalc version 12.2.1.0 (Belgium).

Results

In the 94 RA patients, median disease duration was 27 months (range 1–432 months). Fifty of them were IgM RF positive. Ten out of 94 patients (10.6%) showed bone fusions (Fig. 1) in comparison with two (one patient with gout and one with PsA) out of the remaining 113 subjects (1.8%) (χ^2=5.9, p=0.015). RA patients with fusions had longer disease duration [median 77.5 months (range 1–432 months) *vs*. 22.5 months (1–360 months), p=0.019]. DAS 28 was similar in the two groups (4.6±2 *vs*. 4.2±1.6); age, gender, number of tender and swollen joints, ESR, CRP, and IgM RF levels were also similar (Table I). Bone fusions in RA patients occurred more frequently between the 2nd metacarpal base and trapezoid, trapezium and trapezoid, 2nd and 3rd metacarpal bases, 4th metacarpal base, hamate and capitate (Fig. 2). Of the two control patients with bone fusion, one was a 30-year-old man affected by gout who showed it between hamate and capitate, and between 2nd metacarpal base and trapezoid. The second patient was a 19-year-old man with PsA and bone fusion between 2nd metacarpal base, trapezoid and capitate. Patients with psoriatic arthritis had median disease duration of 60 months (range 1–232 months) and a mean DAS 28 of 3.4±1.4. Disease duration was similar to that observed in RA patients whereas DAS 28 was slightly lower (p=0.04).

Discussion

This is the first study to systematically investigate ankylosis in the wrist of RA patients by MRI.

Ankylosis was a rather frequent lesion, occurring in about 10% of RA patients in comparison with less than 1% of those studied by conventional radiography (1). MRI is more sensitive than conventional radiography to evaluate erosions thanks to its multiplanar imaging capacity (16). The same rule should apply also for joint ankylosis. MRI sensitivity for bone lesions is obviously related to the number (and thickness) of the slices obtained during the examination. The type of sequence employed in our study allowed a minimum slice thickness of 0.6 mm without gap, implying that in the coronal plane about 60 slices of the wrist could be analysed. This degree of sensitivity is a good omen for the identification of all areas involved by ankylosis.

Bone ankylosis seems to be peculiar to RA and related to disease duration. Conversely, it was not associated with disease severity in our study. Contrary to our previous expectation, bone ankylosis was more frequent in RA than in PsA. This may be ascribed in part to the small number of patients with PsA. Disease duration was higher in PsA patients, a fact that should have

Table I. Demographic and clinical features of rheumatoid arthritis patients with and without bone ankylosis of the wrist at MRI.

Feature	Ankylosis +	Ankylosis –	*p*
Gender	5M/5F	22M/62F	0.23
Age (years)	54.7 ± 16.9	53.62 ± 16.2	0.92
Disease duration (months)	77.5 (1–432)	22.5 (1–360)	0.019
DAS 28 CRP	4.64 ± 2.00	4.15 ± 1.6	0.39
IgM RF (IU)	108 (6–150.6)	40.5 (0–2660)	0.17
IgM RF present/absent	7/10 (70%)	43/84 (51.2%)	0.43
ESR (mm/h)	13.5 (2–98)	40.7 (2–120)	0.12
CRP (mg/dL)	18.5 (2.5–100)	10 (0.5–128)	0.47
Number of tender joints	12 (0–28)	6.5 (0–28)	0.41
Number of swollen joints	6.5 (0–25)	5 (0–28)	0.72

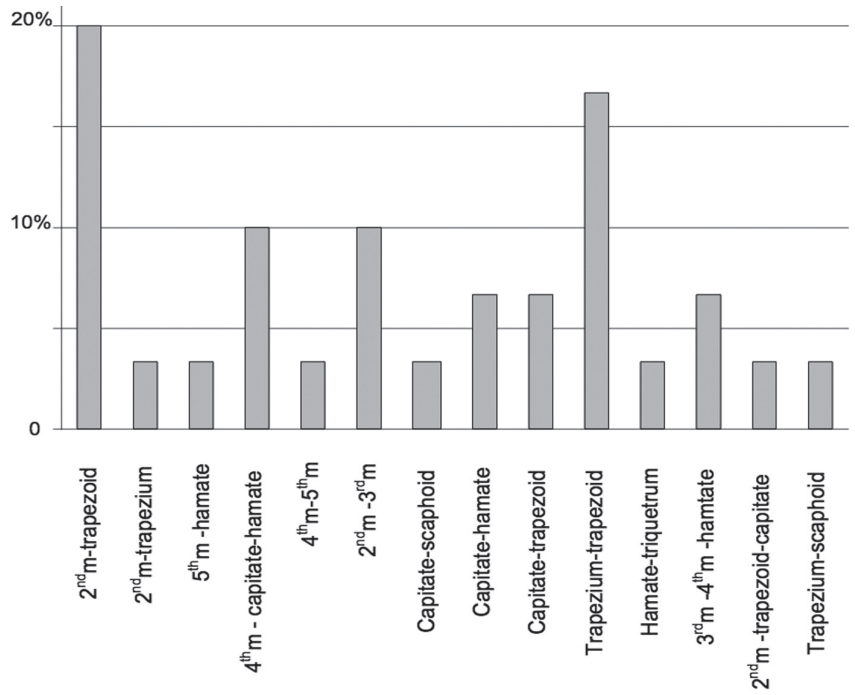

Fig. 2. Frequency of MRI-evaluated ankylosis of the wrist bones in patients with RA (m=metacarpal).

favoured ankylosis development in this group of patients. The association between disease duration and ankylosis in RA could be explained by the fact that patients with longer history of RA could be affected by juvenile chronic arthritis, a condition where ankylosis of the cervical spine has been frequently observed (17). Of the 10 patients with RA and ankylosis, however, none had disease onset before 16 years of age. Whereas bone ankylosis was discovered at a mean age of 54 years in RA, it was seen in two young control patients with gout and PsA of 30 and 19 years of age, respectively.

Our original hypothesis that wrist ankylosis could result from low disease activity with a consequent reparative processes was not supported by our findings. No difference was observed in DAS 28 between RA patients with or without bone ankylosis. The main explanation is of course that no relationship exists between ankylosis and a low level of local inflammation. Alternatively, we could speculate that one single cross sectional determination of DAS 28 at the time of MRI is not a sufficient indicator of the behaviour of RA during bone ankylosis development. Therefore the area under the curve of DAS 28 over time could be a better indicator, but this information was unfortunately not available for the majority of our patients. In addition, DAS 28 is a reliable index of disease activity in general, but does not necessarily reflect the intensity of inflammation in a specific joint. It has been demonstrated that synovitis activity may vary within the same joint, with a patchy histological localisation.

In conclusion, our results support the view that bone ankylosis in RA is related to the duration of disease rather than to its severity. When studied by a sensitive method, such as MRI, this lesion is more frequent in RA than previously believed. Bone ankylosis is not limited to seronegative spondyloarthritides, but may be part of the bone damage observed in RA.

Acknowledgements

We thank Carlo M. Pesce, MD, Associate Professor of Pathology for reviewing the manuscript.

References

1. LEDEN I, THEANDER J, SVENSSON B: Small joint ankylosis in rheumatoid arthritis: a vanishing phenomenon or a pathogenetic clue, or both? *Ann Rheum Dis* 2008; 67: 1786-7.
2. SCHETT G, COATES LC, ASH ZR, FINZEL S, CONAGHAN PG: Structural damage in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: traditional views, novel insights gained from TNF blockade, and concepts for the future. *Arthritis Res Ther* 2011; 13 (Suppl. 1): S4
3. VISSER H, LE CESSIE S, VOS K, BREEDVELD FC, HAZES JM: How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. *Arthritis Rheum* 2002; 46: 357-65.
4. HALVORSEN EH, HAAVARDSHOLM EA, POLLMANN S *et al*.: Serum IgG antibodies to peptidylarginine deiminase 4 predict radiographic progression in patients with rheumatoid arthritis treated with tumour necrosis factor-alpha blocking agents. *Ann Rheum Dis* 2009; 68: 249-52.
5. DIARRA D, STOLINA M, POLZER K, ZWERINA J, OMINSKY MS, DWYER D: Dickkopf-1 is a master regulator of joint remodeling. *Nat Med* 2007; 13: 156-63.
6. LORIES RJ, DERESE I, DE BARI C, LUYTEN FP: Evidence for uncoupling of inflammation and joint remodeling in a mouse model of spondylarthritis. *Arthritis Rheum* 2007; 56: 489-97.
7. BARBIERI F, PARODI M, ZAMPOGNA G, PAPARO F, CIMMINO MA: Bone ankylosis of the wrist as possible indicator of treatment efficacy in rheumatoid arthritis. *Rheumatology* (Oxford) 2010; 49: 1414-6.
8. KWONG FN, HARRIS MB: Recent developments in the biology of fracture repair. *J Am Acad Orthop Surg* 2008; 16: 619-25.
9. SCHWARTZ S: Localized fusion at the wrist joint. *J Bone Joint Surg Am* 1967; 49: 1591-6.
10. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
11. TAYLOR W, GLADMAN D, HELLIWELL P, MARCHESONI A, MEASE P, MIELANTS H: Classification criteria for psoriatic arthritis: development of new criteria from a large international study [CASPAR]. *Arthritis Rheum* 2006, 54: 2665-73.
12. WALLACE SL, ROBINSON H, MASI AT, DECKER JL, MCCARTY DJ, YŰ TF: Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum* 1977; 20: 895-900.
13. BIRD HA, ESSELINCKX W, DIXON AS *et al*.: An evaluation of criteria for polymyalgia rheumatica. *Ann Rheum Dis* 1979; 38: 434-39.
14. SCOTT IC, SCOTT DL: Joint counts in inflammatory arthritis. *Clin Exp Rheumatol* 2014; 32 (Suppl. 85): S7-S12.
15. ØSTEERGARD M, MØLLER-BISGAARD S: Optimal use of MRI in clinical trials, clinical care and clinical registries of patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2014; 32 (Suppl. 85): S7-S12.
16. EJBJERG BJ, VESTERGAARD A, JACOBSEN S, THOMSEN H, ØSTERGAARD M: Conventional radiography requires a MRI-estimated bone volume loss of 20% to 30% to allow certain detection of bone erosions in rheumatoid arthritis metacarpophalangeal joints. *Arthritis Res Ther* 2006; 8: R59.
17. LAIHO K, SAVOLAINEN A, KAUTIAINEN H, KEKKI P, KAUPPI M: The cervical spine in juvenile chronic arthritis. *Spine J* 2002; 2: 89-94.