Severely destructive unilateral wrist arthritis as a rare variant of rheumatoid arthritis: analysis of clinical and imaging features

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Abstract

Objective

Rheumatoid arthritis (RA) is a common autoimmune disease typically affecting joints symmetrically. A small number of patients develop unilateral and severely destructive wrist arthritis (DWA). The objective of our study was to characterise patients with this type of affection.

Methods

This was a retrospective cohort study of RA patients with positive RF/anti-CCP antibodies. *Clinical characteristics, including, age, gender, disease duration, dexterity, occupational history, smoking status, and the number of prescribed DMARDs were recorded. Conventional radiographs were evaluated using the modified Sharp/van der Heijde scoring (mSS) method.*

Results

We analysed our laboratory database of 1247 patients and identified 559 patients with a clinical diagnosis of RA. For 395 of the patients, radiographs of the hands were available for evaluation. 25 patients had extensive unilateral DWA, corresponding to a prevalence of 6.3% (25 of 395 patients). 11 patients were excluded due to incomplete data. Of the remaining 14 patients, 13 were female with a median age of 61 (33–83) years, and median disease duration of 18 (1–33) years. 8 of 11 (72.7%) patients were smokers; in three, smoking status was not known. 80% with known dexterity developed unilateral DWA in the dominant hand. Total mSS was significantly higher on the affected side (39, interquartile range 35.25–46.25) versus non-affected (13, IQR 3–23). MSS were not different if the carpal bones were excluded from scoring. Side of involvement (left vs. right), or dominant versus non-dominant hand, did not result in a different mSS.

Conclusion

Unilateral DWA is a rare variant of RA which predominantly affects women who smoke.

Key words

rheumatoid arthritis, imaging, rheumatoid factor, cyclic citrullinated peptide, radiography

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Introduction

Rheumatoid arthritis (RA) affects about 1% of the general population and is a chronic erosive inflammatory arthropathy usually characterised by the symmetrical involvement of small and large joints (1). The disease course and prognosis have been improved substantially in the last two decades due to the development of novel disease-modifying anti-rheumatic drugs (DMARDs) (2). Nowadays, the available medications, including conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDs (tsDMARDs), and biological DMARDs (bDMARDs) have not only allowed to achieve clinical remission or low disease activity in many patients, but also to halt the radiographic progression and joint destruction, or even favour the repairing process of joint erosions (3, 4). In a proportion of patients, the disease progresses nevertheless and leads to joint destruction (5). Occasionally, wrist arthritis causes severe destruction of the carpal bones with ankylosis and is then termed "os carpale". Severely destructive wrist arthritis (DWA) has only rarely been reported in the literature in juvenile idiopathic arthritis (JIA) (6) but has not been systematically assessed in RA. Symmetric DWA has been described in patients with a given diagnosis of "seronegative RA" (7). Asymmetrical joint involvement is a characteristic feature of spondyloarthropathies, particularly psoriatic arthritis (PsA), but is atypical of RA. Herein, we report our experience of antibody-positive RA patients with a severe, but predominantly *unilateral* DWA at our centre. Since there are only few reports of this pattern, we systematically screened a large cohort of well-characterised RA patients fulfilling the ACR/EULAR criteria for the presence of this variant to better understand factors associated with its occurrence.

Materials and methods

Patient population and data collection

This was a single-centre retrospective cohort study using routine clinical data. First, we screened our laboratory database from 2011 to 2017 to identify all patients with positive rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (CCP) antibodies (abs). RF was determined using the EliA™ RF-IgG assay (Phadia, Thermo Scientific), anti-CCP antibodies were determined either using the EliA™ CCP assay (Phadia, Thermo Scientific) or Abbott Architect (Abbott Laboratories). Anti-nuclear antibody immunofluorescence titres were measure using the EUROPLUS™ ANA-Mosaik 20A assay (Euroimmun). Additional antibodies against extractable antigens (ENA) were detected using the EliA Symphony S assay (Phadia, Thermo Scientific). Then, we determined the number of patients with available conventional radiographs of both hands and wrists for evaluation. Only patients with unilateral DWA, as defined by ankylosis of the carpal bones on one side but not the other, were further evaluated in the study. We included only antibody (RF and/or anti-CCP) positive adult patients with RA. We obtained epidemiological data, including age, gender, disease duration, dexterity, smoking history, and occupation for all patients as well as past and current treatments. Patients with antibody-negative RA, post-traumatic osteoarthritis, and patients with a personal or family history of PsA were excluded.

Scoring of conventional radiographs (modified Sharp/van der Heijde method)

To quantify the involvement of the hands and wrists, we evaluated conventional radiographs according to the modified Sharp/van der Heijde method (henceforth referred to as modified Sharp score, "mSS") (8). Available radiographs of both hands were assessed simultaneously by a team of two investigators (one rheumatology fellow [VK] and one board-certified radiologist JF]). The mSS takes into account 16 joints for possible erosions and 15 joints for joint space narrowing (JSN). Erosions (0–5 points) and JSN (0–4 points) are evaluated separately, consequently retrieving a maximum of 160 points for erosions and 120 points for JSN for both hands. The following regions were analysed for erosions: Proximal interphalangeal (PIP) joints 2–5, interphalangeal (IP) joint 1, metacarpophalangeal (MCP) joints 1-5, carpo-

metacarpal (CMC) 1, os trapezium, os trapezoideum, os scaphoideum, os lunatum, distal radius, and ulna. JSN was evaluated in the following areas: PIP 2-5, MCP 1-5, CMC 3-5, scaphoideum-trapezium, scaphoideum-capitatum, and radiocarpal joints, as previously described (8). Comparisons between the affected side *versus* the unaffected side were performed. Since it was expected that the total mSS would be higher on the side of the DWA based on the study question, the mSS was also assessed for both hands with the exclusion of carpal bones and adjacent joints. In addition, we investigated the mSS depending on the side where DWA occurred (left or right), and compared these results with hand dominance (dominant *vs*. non-dominant hand).

Statistical analysis

Epidemiological data were assessed using descriptive statistics. Comparisons between the two groups were carried out using the Mann-Whitney test for non-parametric values. All statistical analyses were performed with GraphPad Prism (v. 8.2.1 for macOS, GraphPad Software, San Diego, CA, USA, "www.graphpad.com").

Results

Patient characteristics

Our database search yielded 1247 patients with either positive RF, anti-CCP abs, or both. A diagnosis of RA was confirmed in 559 patients based on a documented clinical diagnosis according to ACR/EULAR criteria; conventional plain radiographs of the hands were available in 395 eligible patients. After the evaluation of conventional radiographs and exclusion of 370 patients due to symmetric or no wrist involvement, we included 25 patients. Of these, we excluded 11 due to incomplete clinical data (Supplementary Fig. S1). All but one of the remaining 14 patients were female (92.9%). The median age was 61 years (range 33–83), median disease duration was 18 years (range 1–33). First occurrence of DWA was estimated as the time between the first diagnosis of RA and the first radiograph in which DWA was detectable. Median time of DWA occurrence was 12 years (ranging from 0 to 26 years). Nine patients were right-handed, one was left-handed, in four patients, dexterity was not known. Eight patients were smokers; three patients were non-smokers; in three patients, smoking status was not known. Median anti-CCP abs levels were 94.6 IU/ml (normal range [NR] <5, interquartile range [IQR] 18–299.5), median RF 54.2 IU/mL (NR <16, range 21.55–263.33). All but three patients were positive for both antibodies; however, in four patients, anti-CCP abs were only weakly positive (15, 11, 6, and 19, respectively). RF was negative in three patients. HLA B27 status was unknown in the majority of patients (twelve of 14) and negative in the remaining two. ANA abs were positive in eight of 14 patients, but there was no clear pattern of ENA abs: one patient tested positive for anti-Histone abs, one for anti-PmScl, and a third patient for anti-SSA. In eight of ten (80%) of patients with known dexterity, DWA occurred in the dominant right hand. In 2/10 (20%) patients, destruction occurred in the non-dominant hand. Patients received a median number of 3 (range 1–6) DMARDs, mainly conventional synthetic. Demographic and clinical data are summarised in Table I.

Imaging features

Based on the study question, only patients with severely DWA were analysed. Figures 1A and B show a representative conventional radiograph (CR) of the hands with severe destruction of the carpal bones (right side in this example). Radiographic scoring of the hands showed a total mSS of the affected *versus* non-affected hand of 39 (interquartile range [IQR] 35.25–46.25) *versus* 13 (IQR 3–23) (Fig. 1C, $p<0.0001$). To evaluate the mSS without the carpal bones and adjacent joints, only the scores for the IP joint 1, MCP joints 1–5, and PIP joints were evaluated for erosions and JSN. There was no difference between both hands when bony wrist structures were not taken into account (Fig. 1D, mSS of 6.5 [IQR 4.75-10.5] *versus*. 6.5 [IQR 0-12.5], not statistically significant). Since most, but not all patients had an affection of their dominant hand, we assessed whether there were differences in the mSS between the left and right hand (independent of hand dominance) and found that the side of involvement did not affect the total mSS (Fig. 1E, 38 [IQR 30.25–46.25] *vs*. 43 [IQR 36.25-48.75] for the left *vs*. the right hand, no statistical difference). Ultimately, we compared whether the total mSS differed depending on the affection of the dominant *versus* the non-dominant hand (Fig. 1F). In seven of ten patients, the dominant hand was affected, whereas three patients had an affection of the non-dominant hand. In four patients, dexterity was not known. Again, this did not result in any statistical difference (mSS 42 [IQR 36–45] for the dominant hand *vs*. 38 IQR 25–65] in the non-dominant hand.

Discussion

Our study aimed to characterise RA patients who developed carpal arthritis in an unusual, asymmetrical pattern and to describe imaging findings. Our results suggest that this type of joint involvement predominantly occurs in female patients who smoke, and tend to occur in the patients' dominant hand. Of note, none of the patients in our cohort had heavy physical working conditions. To our knowledge, this is the first study that systematically analysed a cohort of 395 antibody-positive, classification criteria fulfilling RA patients with unilateral DWA as per our definition. The clinico-radiographic findings identified in this group of patients represent a unique phenotype of RA, unique in that it steers away from the "classic" RA phenotype of symmetrical erosive joint disease of either small joints or a symmetric affection of the carpal bones ("os carpale").

A review of the literature identified only few studies, case reports or case series with a similar phenotype across various rheumatic conditions. One of the previously published retrospective studies described a chronic DWA in two anti-Ro/SS-A positive patients among 340 analysed patients with different autoimmune diseases, including RA, systemic lupus erythematosus, systemic sclerosis, overlap syndrome, Sjögren's syndrome, and others (9).

Table I. Epidemiologic and clinical characteristics of the patient population.

Patient	Age, Sex	Disease duration (years)	Affected hand	Dexterity	Smoker	Occupation	Antibodies	HLA-B27 / ANA status	Additional clinical manifestations	Previous treatments	Current treatment
1	60, F	18	L	R	Y	Mechanic	CCP(+)/RF-	HLA B27 UKN, ANA 1:320 (ULN 1:80), SSA 235 U/ml (ULN 7 U/ml)	Secondary Sjogren's syndrome	HCQ, MTX, ETN, ADA, RTX	GOL
2	54, F	8	L	R	Y	Childcare	CCP+/RF+	HLA B27-, ANA-	None	SSZ, LEF, MTX	ETN
3	55, F	12	R	R	Y	Teacher	CCP+/RF+	HLA B27 UKN, ANA 1:100 (ULN 1:100), ENA-	None	SSZ, LEF, ETN, ATC	MTX+RTX
4	54, F	13	R	R	Y	Florist	CCP+/RF+	HLA B27 UKN, ANA UKN	None	MTX	MTX+ETN
5	62, F	1	R	R	UKN	Florist	CCP(+)/RF-	HLA B27-, ANA 1:1000 (ULN 1:100), ENA-	None	MTX, LEF, ETN, ADA	TOFA
6	56, F	7	R	R	Y	Seller	CCP+/RF+	HLA B27 UKN, ANA 1:80 (ULN 1:80), ENA UKN	None	MTX, CHQ, ADA, TCZ, RTX	BARI
7	33, F	18	L	UKN	UKN	UKN	CCP+/RF+	HLA B27 UKN, ANA UKN	None	MTX, SSZ, HCQ, LEF; ETN, ADA	TCZ
8	70, F	22	L	L	N	Office worker	CCP+/RF+	HLA B27 UKN, ANA-	None	ADA	MTX+BARI
9	67, F	22	L	UKN	N	Florist	CCP(+)/RF+	HLA B27 UKN, ANA 1:320 (ULN 1:100), Histone 66 U/ml (ULN 15 U/ml)	None	HCQ, MTX, ADA	ETN
10	70, F	22	R	R	Y	Office worker	CCP+/RF+	HLA B27 UKN, ANA 1:1000 (ULN 1:100), Pm-Scl 80 U/ml (ULN<7 U/ml),	Pulmonary fibrosis; RA-ILD or possible overlap with Systemic sclerosis sine scleroderma	SSZ, MTX, AZA	LEF
11	45, F	24	L	UKN	Y	Office worker	CCP(+)/RF+	HLA B27 UKN, ANA-	None	MTX	UKN
12	76, F	22	R	R	Y	Kitchen manager	CCP+/RF-	HLA B27 UKN, ANA 1:320 (ULN 1:100)	None	MTX, LEF	MTX+RTX
13	73, M	33	R	UKN	UKN	UKN	CCP+/RF+	HLA B27 UKN, ANA 1:80 (ULN 1:80), ENA-	None	MTX	MTX+RTX
14	83, F	8	R	R	N	UKN	CCP+/RF+	HLA B27 UKN, ANA-	None	LEF	ADA

ADA: adalimumab; ANA: anti-nuclear antibodies; ATC: abatacept; AZA: azathioprine; BARI: baricitinib; CCP: anti-cyclic citrullinated peptide antibodies; CHQ: chloroquine; ETN: etanercept; F: female; GOL: golimumab; HCQ: hydrxychloroquine; HLA: human leukocyte antigen; LEF: leflunomide; M: male; MTX: methotrexate; Pm-Scl: anti polymyositis-scleroderma antibody; RA-ILD: rheumatoid arthritis-intersititial lung diseases; RF: rheumatoid factor; RTX: rituximab; SSA: anti-Sjögren's syndrome A antibody; SSZ: sulfasalazine; TCZ: tocilizumab; TOFA; tofacitinib; UKN: unknown; ULN: upper limit of normal.

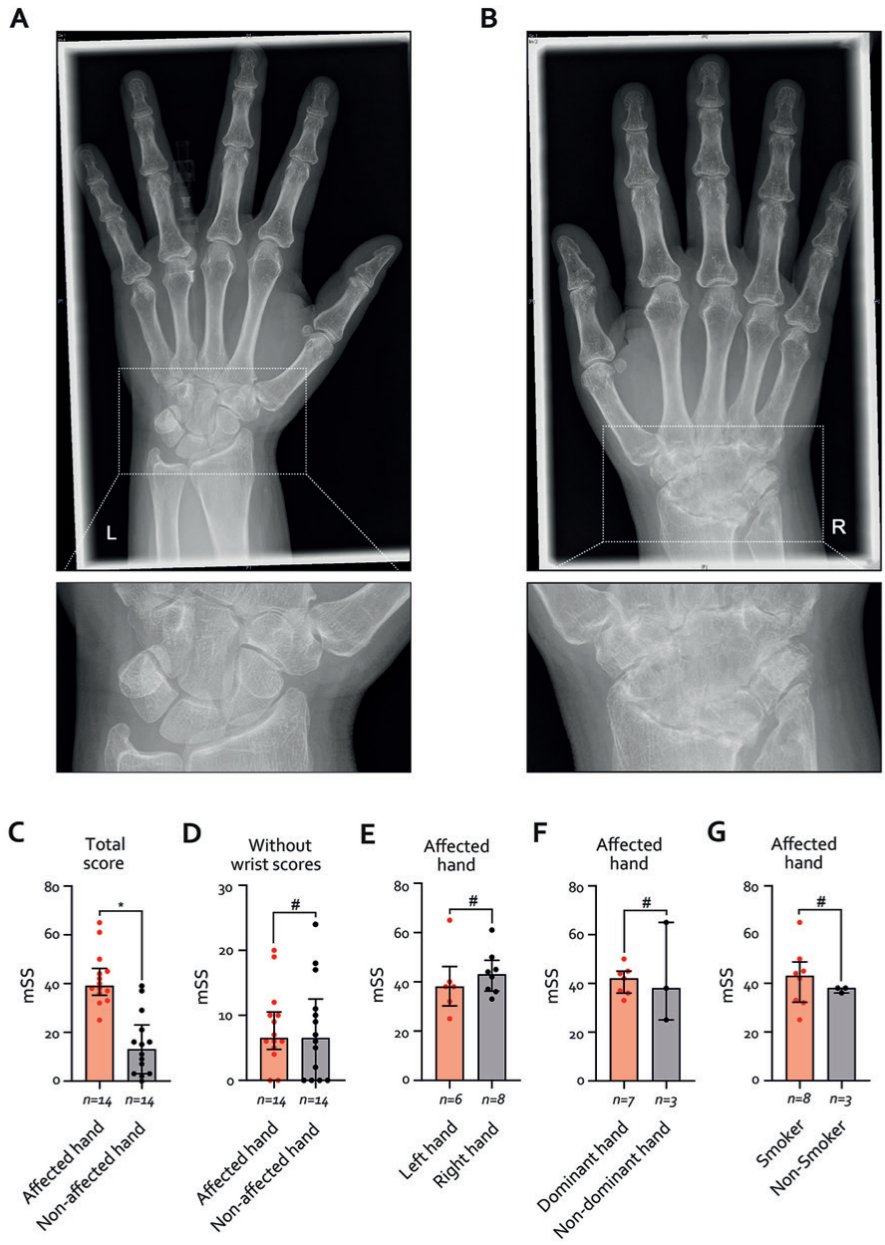

Fig. 1. Radiographic presentation of destructive unilateral wrist arthritis and scoring according to the modified Sharp/van der Heijde method.
A-B: Representative conventional radiograph of the hands. The right carpus **(B)** shows severe ankylosis and erosions compared to the unaffected left side **(A)**. Of note, the metacarpophalangeal and proximal interphalangeal joints are relatively spared. **C**: Total modified Sharp score (mSS) of the affected *versus* the non-affected hand. The median mSS of the affected side is 39 (interquartile range [IQR] 35.25–46.25) *versus* 13 (IQR 3–23) of the non-affected hand (*p<0.0001). **D**: Total mSS without scoring the carpal joints. There is no difference when the carpal structures are not taken into account (affected hand 6.5 [IQR 4.75–10.5] *vs*. 6.5 [IQR 0–12.5] in the non-affected hand). **E**: Total mSS of the left *versus* the right hand. The median mSS is 38 (IQR 30.25–46.25) *versus* 43 (IQR 36.25–48.75) for the left and the right hand, respectively. **F**: Total mSS comparing the affection of the dominant *versus* the non-dominant hand. There was no statistical difference when the dominant or non-dominant hands were affected by DWA (mSS 42 [IQR 36–45] for the dominant hand *versus* 38 [IQR 25–65]. Of note, in four patients, dexterity was not known. **G**: Total mSS of the affected in smokers *versus* non-smokers. There was no statistical difference in the mSS of smokers *versus* non-smokers (43 [IQR 32.25–48.75] in smokers *versus* 38 [IQR 36–38]). In three patients, smoking status was not known.

Another retrospective study assessed 250 juvenile idiopathic arthritis patients, six of whom developed an asymmetric DWA. Interestingly, of these six patients, five had positive antinuclear antibodies, and one patient a positive RF. This study also showed that the grade of radiographic destruction in 2 ANA-positive patients with the longest duration of the disease was similar to RF-positive patients (6).

Nikiphorou *et al*. described four seronegative RA patients with unilateral destructive arthritis of the wrist, subtalar, ankle, and large joints, although not primarily focusing on the wrist joints (7). Of note, two of four patients in this report were positive for HLA B27 but without signs of sacroiliitis.

Another case report of a patient with adult-onset Still's disease showed bilateral subchondral erosions and JSN in the small hand joints bilaterally along with severe ankylosis of the right wrist joint (10). Destructive wrist and elbow arthritis have also been reported in a case of Crohn's disease (11). Not surprisingly, unilateral DWA has also been described following infectious arthritis secondary to tuberculosis (12).

The process of wrist destruction is usually insidious; therefore, patients may adapt well to the resulting functional deficit (13). As many as 95% of RA patients develop bilateral involvement of wrist joints ten years after disease onset (14). The exact pathogenesis of site-specific involvement is not known. A possible explanation could be a site-specific pattern of expressed inflammatory mediators, which form an intraarticular microenvironment, as well as mechanical stress, embryonic development patterns, and epigenetic mechanisms (15). The predisposition to the development of unilateral destructive arthritis on the dominant hand suggests that chronic repetitive injury may contribute to its development. The high number of DMARDs (median number of 3) used in our cohort, including bDMARDs, does not seem to prevent the development of unilateral DWA. In fact, it may indicate failure to respond to these treatments, in other words, a more refractory or resistant disease process.

Considering the low prevalence of unilateral DWA in our cohort of RA patients, it is difficult to predict the risk of progression in an individual patient. However, early identification of unilateral wrist destruction using CR, along with characteristic imaging features, could imply that other measures than

medical therapy with DMARDs, such as local glucocorticoid injections, may be required in this particular phenotype.

There are significant limitations in our study: CR has a low sensitivity compared with magnetic resonance imaging or computed tomography to visualise joint erosions, especially in the carpal bones, and is, therefore, a limitation in the assessment of the mSS (16). Also, we excluded seronegative RA patients to avoid any misclassification bias. Since our cohort of patients with a confirmed diagnosis of RA consisted of a sizable number of patients, the small number of patients may well reflect the prevalence of this phenotype in a given RA population.

In conclusion, this is, to our knowledge, the first study in a well-characterised RA population that systematically assessed clinical and imaging features of severely DWA. The data obtained support the hypothesis that certain factors may contribute to the clinical pattern of autoimmune diseases: in our cohort, these were mainly female gender and smoking.

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