

Ultrasound imaging for the rheumatologist XLVIII. Ultrasound of the shoulders of patients with rheumatoid arthritis

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ABSTRACT

Objective. To investigate the prevalence of ultrasonographic (US) shoulder abnormalities in patients with rheumatoid arthritis (RA) and to investigate the relationship between US findings and demographic and clinical features.

Methods. Consecutive patients attending the rheumatology units involved in this study were enrolled. Clinical and demographical data were recorded. US of bilateral shoulders was performed at the same time, examining tendons, bursae, gleno-humeral and acromion-clavicular joints. The presence of signs of inflammation, bone erosions or rotator cuff pathology was evaluated.

Results. A total of one hundred patients were enrolled, mean age (SD) 59.6 (14.7) years, median disease duration (IQR) 56.5 (34.7, 96.5) months, 98% of them were on DMARDs and 22% on biologics. Shoulder tenderness was reported by 44% of patients. 34% of patients showed at least one sign of inflammatory involvement, and 25% of them presented with humeral head erosions. Signs of rotator cuff pathology were seen in 49% of patients. Agreement between the presence of spontaneous pain and US inflammatory abnormalities was moderate (kappa 0.501). Patients with inflammatory involvement of the shoulders had significantly higher DAS28, HAQ, VAS pain, acute phase reactants and disease duration compared to patient with no inflammatory signs, they were more frequently RF positive and reported more frequently spontaneous pain.

Conclusion. US assessment of the shoulder in RA patients can be considered of value, especially in patients with relevant indicators of disease activity and severity.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that involves mainly synovial joints. The natural history of RA includes persistent joint inflammation leading to the deterioration of articular structures and to the subsequent development of irreversible disability (1).

Although the disease more frequently involves small joints, large joint involvement is not uncommon, and this has been related to higher levels of disability and poor outcome (2, 3). In RA, shoulder involvement is common, with several structures that can be targeted by the disease and with an impact on physical function (4, 5). The gleno-humeral joint (GHJ) can be involved, but also periarticular structures such as the long head of the biceps tendon (LHBT) or the subacromial/subdeltoid bursa (SAD) can undergo inflammatory processes.

In the literature, up to 5% of patients after 2 years and 96% after 12 years showed erosive damage at the shoulder (6, 7). Nevertheless, only a small proportion of patients has clinically detectable shoulder tenderness (18.5%) and swelling (8).

Clinical evaluation of the shoulder does not allow an accurate assessment of this structure (9). In a study performed on 50 patients with RA, a poor relationship between effusion detected on physical examination and confirmed by ultrasonography (US) was demonstrated, with a kappa value of 0.202 (10).

Musculoskeletal US has proved to be a valid tool in the assessment of inflammatory arthritis, including RA (11, 12). US has proved to be more sensitive than clinical examination (13) and has also shown responsiveness to change, along

Competing interests: none declared.

with clinical and laboratory measures (14).

A study examining the agreement between US and MRI of shoulder findings demonstrated a high agreement on erosions, moderate agreement on grey-scale (GS) findings, depending on the structure examined, and higher agreement for power Doppler (PD) findings (15). In the context of the evaluation of a US score based on large joints, GS shoulder abnormalities decreased significantly after the institution of efficacious treatment, while PD did not (16).

The aim of the present study was to evaluate the frequency of US-detectable abnormalities in the shoulders of patients with RA, taking into account inflammatory alterations, signs of bone damage and of rotator cuff pathology. In particular, the correlation between inflammatory lesions and clinical features was investigated.

Patients and methods

Clinical evaluation

A total of 100 patients with RA, classified according to the 1987 ACR (17) or, alternatively, the 2010 ACR/EULAR classification criteria (18), attending four outpatients rheumatology clinics in Italy, were consecutively enrolled. Patients with severe shoulder trauma and joint surgery were excluded from this study. An expert rheumatologist evaluated patients in each center, collecting clinical and laboratory data and performing a joint count on 28 joints and calculating DAS28 (19). Moreover, the presence of spontaneous joint tenderness and pain during acromion-clavicular palpation were recorded. Provocative maneuvers (the Hawkins, Jobe, Patte, Gerber, and Speed tests) were performed as well (20). All patients gave written consent before the inclusion in the study, which was conducted according to the principles of the Declaration of Helsinki.

Ultrasonographic evaluation

US assessment was carried out at each centre by a single experienced operator who was blinded to clinical findings, in the same day of clinical evaluation. Before the beginning of the study, all operators reached an agreement on

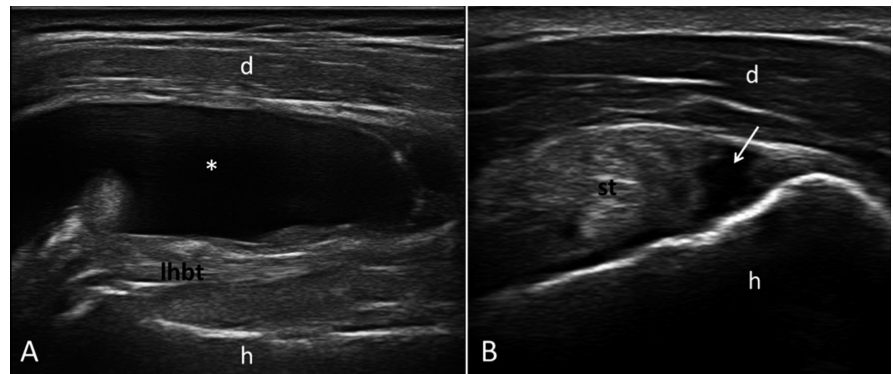


Fig. 1. A. Subdeltoid bursitis (asterisk). B. Supraspinatus tendon tear (arrow). lhbt: long head of the biceps tendon; st: supraspinatus tendon; d: deltoid; h: humerus.

both the scanning technique and the definition of pathology. The scanning technique was defined based on international indications and guidelines (21-25). US examinations were carried out using a MyLab 70 scanner (Esaote SpA, Genoa, Italy) equipped with a linear multifrequency probe, operating at 4-13 MHz, and a Logiq 9 machine (General Electrics Medical Systems, Milwaukee, WI, USA) with a linear probe operating at 9-14 MHz.

Articular and peri-articular shoulder structures were examined, in particular the SAD bursa, the sheath of the LHBT, the axillary and posterior recesses of the GHJ and the acromion-clavicular joint (ACJ) were examined for the presence of synovial effusions (SE) and synovial hypertrophy (SH). Power Doppler (PD) assessment of the synovial sites, including LHBT, the SAD bursa, and the GHJ, was carried out under standardised settings (pulse repetition frequency 750 Hz, Doppler frequency 7.5 MHz, low wall filters, gain at the level that avoided random noise artifacts). For analysis purposes, inflammatory alterations were defined as presence of effusion, synovial hypertrophy or PD at the GHJ, LHBT and SAD bursa. ACJ was not evaluated in this context, since abnormalities at this level are frequently seen even in healthy subjects and might not reflect RA involvement (26).

Moreover, the ACJ was examined for osteophytes as well as fibrocartilage calcifications and the GHJ for the assessment of labrum calcifications and erosions, the presence of PD signal within the erosion was also evaluated. The supraspinatus, infraspinatus, sub-

scapularis tendons were also examined, to evaluate the presence of rotator cuff pathology. In particular, the presence of tendinosis, partial or total tendon tears and calcifications was assessed. Finally, the greater and lesser tuberosity regions were analysed for the presence of local enthesophytes.

Statistical analysis

Descriptive results are reported as absolute and relative frequency for categorical data, and as median (IQR) or mean (SD) according to their distribution. Concordance between clinical and US shoulder involvement was calculated by unweighted kappa-statistics. The association between US involvement and clinical variables was systematically investigated. Categorical variables were analysed using chi-squared tests, quantitative variables were analysed using the unpaired *t*-test for normally distributed, and Mann-Whitney U-test for non-normally distributed variables. All analyses were performed using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium, 2013).

Results

In total, 100 patients were included in this study and 200 shoulders evaluated. Patients had a mean age (SD) of 59.6 (14.7), a median disease duration of 56.5 months, 74% of them were female (Table I). The majority of patients (98%) were on DMARDs, and 22% of them were treated with biologics, in particular 18% with a TNF- α inhibitor and 4% with tocilizumab. One patient was receiving intravenous immuno-

Table I. Baseline characteristics of patients.

Patients (n)	100
Age, mean (SD)	59.6 (14.7)
Male/female (n)	26/74
Disease duration, months, median (IQR)	56.5 (34.7,96.5)
DAS28, mean (SD)	3.31 (1.44)
HAQ, median (IQR)	0.75 (0.1,2.5)
VAS pain, cm, mean (SD)	3.52 (2.8)
RF, n (%)	61 (61)
ACPA, n (%)	47 (47)
ESR mm/h, mean (SD)	22.23 (15.8)
CRP mg/dl, mean (SD)	0.42 (0.44)
DMARDs, n (%)	98 (98)
Corticosteroids, n (%)	55 (55)
Corticosteroid dose, mg, median (IQR)	2.5 (0.5)
Biologics, n (%)	22 (22)
TNFi, n (%)	18 (18)
TCZ, n (%)	4 (4)
NSAIDs, n (%)	18 (18)
Shoulder pain, n (%)	44 (44)
Positive provocative maneuvers, n (%)	46 (46)

DAS28: disease activity score on 28 joints; HAQ: health assessment questionnaire; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DMARDs: disease-modifying anti-rheumatic drugs; TNFi: TNF- α inhibitors; TCZ: tocilizumab; NSAIDs: non-steroidal anti-inflammatory drugs.

Table II. Prevalence of inflammatory findings in the shoulder. Data referring to the number of shoulders examined are presented.

	Right (n=100)	Left (n=100)	Total (n=200)
<i>Long head of the biceps tendon</i>			
Effusion	28	16	44 (22%)
Hypertrophy	5	4	9 (4.5%)
Power Doppler	4	3	7 (3.5%)
<i>Subdeltoid bursa</i>			
Effusion	18	7	25 (12.5%)
Hypertrophy	8	3	11 (5.5%)
Power Doppler	8	3	11 (5.5%)
<i>Subscapularis bursa</i>			
Effusion	4	3	7 (3.5%)
Hypertrophy	1	0	1 (0.5%)
Power Doppler	0	0	0 (0%)
<i>Glenohumeral joint</i>			
Effusion	9	7	16 (8%)
Hypertrophy	4	1	5 (2.5%)
Power Doppler	1	0	1 (0.5%)
<i>Acromion-clavicular joint</i>			
Effusion	34	25	59 (29.5%)
Hypertrophy	10	7	17 (8.5%)
Power Doppler	5	1	6 (3%)

globulins. Corticosteroids were given to 55% of patients, but the majority of them (46% over the entire cohort) were given low dose steroids (≤ 5 mg/day), with a median dose of 2.5 mg/day; 18 patients were taking NSAIDs. Spontaneous joint pain was reported by 44% of patients, while 30% of patients reported pain during the palpation of the ACJ; provocative maneuvers were positive in 46% of patients.

Table II summarises the main inflammatory findings found in our population. In particular, 19 patients presented with inflammatory involvement of the LHBT, 22 with inflammatory abnormalities of the SAD bursa and 14 with involvement of the GHJ. In total, 34 patients presented with at least one inflammatory alteration at these sites. In 25 patients erosions of the humeral head, with dimensions ranging from

0.6 to 10 mm, were found, in 5 of them PD signal was detectable within the erosion.

ACJ presented inflammatory alterations in 40 patients, but at this site osteophytes and degenerative abnormalities were detected in 51 patients, with calcifications seen in 4 patients.

US alterations indicative of cuff rotator pathology are summarised in Table III. Cuff rotator alterations were not uncommon, since 49 patients presented with at least a single abnormality, supraspinatus tendinosis being the most frequent (41 patients), while subscapularis and infraspinatus tendinosis were found in 23 and 14 patients, respectively. Calcifications occurred in the context of the supraspinatus in 13 patients (with dimensions ranging from 0.2 to 7.2 mm), in the subscapularis in 11 patients (0.2–7.4 mm) and in the infraspinatus in 3 (0.4–1 mm). Acoustic shadowing occurred in 2 cases at the subscapularis and 1 case at the infraspinatus calcification. Tendon tears occurred more frequently at supraspinatus (14 patients), with 4 patients presenting with a complete tear, which was bilateral in 3 cases. The infraspinatus was torn in 8 patients and the subscapularis in 4, with a single case of complete tear for both tendons.

Calcifications at the greater tuberosity were found in 6 patients, while calcification at the lesser tuberosity in 5. Labrum calcification was seen in 2 patients, while humeral head hyaline cartilage calcifications were not found. The agreement between the presence of spontaneous pain and the detection of US inflammatory findings was moderate, with a kappa (95% CI) of 0.501 (0.327, 0.675).

When we evaluated the correlation between the main clinical findings and the presence of inflammatory abnormalities, patients with US inflammatory involvement had a longer median disease duration, were more frequently RF positive, had a higher disease activity and higher acute phase reactants, a higher level of disability and more pain, with an increased frequency of spontaneous shoulder pain and higher median VAS pain. On the other hand, age, gender, ACPA positivity were not significantly

different among the two groups. To test the robustness of these findings, taking into account that effusion can also occur in rotator cuff pathology, a more stringent definition of inflammatory US alterations was applied, considering only patients with evidence of synovial hypertrophy and eventually PD. This small subgroup of only 15 patients had still significantly longer disease duration, higher DAS28, HAQ, VAS pain, ESR and reported more frequently spontaneous shoulder tenderness. Moreover, in this group, the proportion of males was higher (Table IV).

Discussion

With the introduction of new treatments and new treatment strategies, the current aim in the treatment of RA is the achievement of low-disease status and eventually remission (27). In this context, a reliable assessment of disease activity is needed in order to modulate therapy. While several joints and synovial sites are easily accessible by clinical examination, larger joints, such as the hips and the shoulders (26, 28, 29), cannot be evaluated easily. Since US has proven to be reliable in the detection of subclinical activity, its application in the evaluation of large joints might be helpful to evaluate disease activity.

In this study a population of patients with RA has been evaluated clinically and by US. The prevalence of inflammatory findings at the GHJ, LHBT and SAD and subscapularis bursae was higher than recently reported in a sample of healthy subjects (26). In particular PD was not detected in healthy controls, while RA patients showed the presence of PD in some synovial sites. In our populations, PD was detected in only one GHJ, but this is likely due to PD limitations related to the size and the depth of the joint. Moreover, the majority of patients included in this cohort had a long disease duration and was taking effective treatment at the time of evaluation and this might have determined an overall low frequency of PD. For the same reasons, although the detection of humeral head erosions was not uncommon in our population, only a minority of patients presented with

Table III. Prevalence of rotator cuff involvement in the shoulder. Data referring to the number of shoulders examined are presented.

	Right (n=100)	Left (n=100)	Total (n=200)
<i>Supraspinatus tendon</i>			
Tendinopathy	37	24	61 (30.5%)
Calcification	14	11	25 (12.5%)
Tear	12	10	22 (11%)
<i>Infraspinatus tendon</i>			
Tendinopathy	13	6	19 (9.5%)
Calcification	0	1	1 (0.5%)
Tear	8	1	9 (4.5%)
<i>Subscapularis tendon</i>			
Tendinopathy	18	13	31 (15.5%)
Calcification	4	8	12 (6%)
Tear	3	4	7 (3.5%)

Table IV. Correlation between US inflammatory findings and clinical features.

	No US inflammatory abnormalities (n=66)	US Inflammatory abnormalities (n=34)	<i>p</i>	No US synovial hypertrophy (n=85)	US synovial hypertrophy (n=15)	<i>p</i>
Age years, mean (SD)	59.24 (15.38)	59.65 (14.68)	0.86	59.75 (14.87)	59.6 (14.07)	0.86
Male gender, n (%)	20 (30.3)	6 (17.6)	0.26	21 (24.7)	5 (33.3)	0.038
Disease duration, months, median (IQR)	48 (36, 57.4)	90 (61.1, 116.2)	0.0001	48 (36.9, 58)	108 (72, 194.4)	0.0002
RF, n (%)	34 (51.5)	27 (79.4)	0.01	48 (56.4)	13 (86.7)	0.189
ACPA, n (%)	30 (45.4)	17 (50)	0.82	39 (45.9)	8 (53.3)	0.80
DAS28, mean (SD)	2.91 (1.28)	4.08 (1.42)	0.0001	3.10 (1.29)	4.47 (1.68)	0.0005
HAQ, median (IQR)	0.5 (0.1, 1.125)	1 (0.75, 1.5)	0.0004	0.5 (0, 1.625)	1.1 (1, 1.875)	0.0017
VAS pain, cm mean (SD)	2.44 (2.36)	5.61 (2.42)	<0.0001	3 (2.53)	6.46 (2.53)	<0.0001
CRP mg/dl, median (IQR)	0.27 (0.18, 0.34)	0.6 (0.41, 0.81)	0.0002	0.3 (0.23, 0.41)	0.45 (0.16, 1.53)	0.37
ESR mm/h, mean (SD)	18.90 (14.73)	28.67 (16.02)	0.003	20.89 (14.77)	29.80 (19.62)	0.043
Spontaneous pain n (%)	17 (25.7)	27 (79.4)	<0.0001	31 (36.5)	13 (86.7)	0.0009

DAS: disease activity score; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; HAQ: Health Assessment Questionnaire; VAS: visual analogue scale; CRP: C-reactive protein; ESR: erythro sedimentation rate.

active lesions showing PD, while in most of them this was probably a sign of previous disease activity. Otherwise, we may hypothesise that some of these bone erosions were not a pathological findings. Of note, Schmidt *et al.* found bone erosions of >1 mm at the humeral head in almost 25% of shoulders in 102 healthy subjects (30).

On the other hand, the involvement of the tendons of the rotator cuff was not uncommon in patients with RA and tended to occur more frequently on the dominant side. The frequency of infraspinatus and subscapularis involvement in our population was similar to that recently reported in a population

of healthy subjects of corresponding age (26). However, supraspinatus tears were more frequent in RA patients, and this might be explained by the use of systemic or even local corticosteroids in this group.

At the level of ACJ, effusion was seen with comparable frequencies compared to healthy controls with similar age, although RA patients had more frequently synovial hypertrophy at this level and a minority of them also showed PD signal, which was not present in healthy subjects. Osteophytes were seen in RA patients with comparable frequencies to the healthy population (26). These findings suggest a role of US in detect-

ing signs of disease activity in the ACJ, which is also frequently involved in degenerative processes (26).

In our cohort we found the agreement between spontaneous joint tenderness and presence of inflammatory lesions to be moderate (κ 0.501). The agreement was higher than what previously reported for clinical evaluation of effusion, suggesting that clinical history could be more reliable than clinical examination in detecting disease activity at this level (10).

When we evaluated the correlation between some clinical features and the presence of inflammatory signs possibly related to disease activity at the shoulders, the presence of such abnormalities on US seemed to identify a subgroup of patients with more severe disease. Patients with inflammatory alterations at the shoulders had a higher disease activity, as shown by higher levels of DAS28, ESR and CRP, and carried higher levels of disability, as previously reported (2). In our population, RF was more frequently detected in patients with shoulder involvement, while the prevalence of ACPA was similar, and this might be due to an overall lower rate of ACPA positive patients in the cohort. Moreover, the presence of local pain and its overall intensity, measured by the VAS pain, were significantly related to inflammatory shoulder involvement. This results were confirmed also by an analysis based on a more conservative definition of inflammatory US involvement, that was meant to include patients in which abnormalities would more likely be due to RA. This further analysis confirmed higher disease activity and disability, ESR and pain, while male patients were more prevalent. However, the small sample size of this cohort has to be taken into account.

These findings are in keeping with previous works, that identified a relation between shoulder involvement and disease activity and disability (31, 32).

The present study carries some limitations. The cross-sectional design does not allow to evaluate the impact of US findings on relevant outcomes, and the univariate analysis does not take into account the potential presence of con-

founders. However, these results based on a large population confirm the value of US in the assessment of the shoulders in RA patients. In this population, US findings are related to relevant clinical and laboratory parameters. US allows the differentiation between degenerative shoulder lesions and signs of disease activity, and identifies a subgroup of patients with higher disease activity that could benefit from a more aggressive treatment approach.

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