Concise report

Magnetic resonance imaging and musculoskeletal ultrasonography detect and characterize covert inflammatory arthropathy in systemic sclerosis patients with arthralgia

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Abstract

Objectives. Arthropathy, particularly synovial inflammation in SSc, is not well characterized. We explored the role of MRI and musculoskeletal ultrasonography (MSUS) in detecting and characterizing synovial inflammation in SSc patients with arthralgia while comparing the two imaging modalities.

Methods. Seventeen SSc patients with arthralgia and no overt inflammatory arthritis had a baseline MSUS of their hands. Six months later, 13 unselected patients had a second MSUS and 8 of these 13 patients also had MRI with gadolinium of their most symptomatic hand.

Results. Of the eight patients undergoing MRI scan, all (100%) patients had synovitis and 88% of patients had tenosynovitis. MRI also showed erosions in 75% of patients. On MSUS, on baseline and second scans, tenosynovitis was seen in 46% and 47% of the patients and synovitis in 6% and 23%, respectively. No erosions were identified. Applying the RAMRIS system (a semi-quantitative MRI scoring system used in RA), the mean values for synovitis, oedema and erosions fell within the range seen in RA.

Conclusions. This study demonstrates the presence of a persistent inflammatory, erosive, peripheral arthropathy, similar to that seen in RA, in SSc patients with arthralgia without overt inflammatory joint disease. While both MRI and MSUS are useful in characterizing synovial inflammation in SSc, MRI is clearly more sensitive than MSUS in this setting. Further studies to establish the clinical and radiological musculoskeletal outcomes over time in this group of patients are required in order to identify the appropriate management of arthralgia in SSc.

Key words: Systemic sclerosis, Synovial inflammation, Synovitis, Tenosynovitis, MRI, MSUS, Erosions.

Introduction

While arthralgia is common in SSc, its cause is poorly understood. It is usually attributed to mechanical factors resulting from fibrosis, with tendon friction [1]. Erosive changes have been reported on X-rays in some SSc patients [2]; and have been attributed to overlap with mixed CTD [3] or RA. Musculoskeletal ultrasonography (MSUS) and MRI can identify and characterize subclinical synovial inflammation and joint damage with much greater precision than X-rays [4, 5].

We report a study designed to (i) identify the presence and confirm the persistence of subclinical synovial inflammation, utilizing MSUS; (ii) compare the two imaging modalities of MSUS and MRI for characterizing any synovial inflammation; and (iii) correlate synovial inflammation on MRI and/or MSUS with high-sensitivity CRP (hsCRP), a serum marker for low-grade inflammation.
Methods

Patients
Thirty-five consecutive patients meeting ACR (formerly the ARA) classification criteria for SSc [6] without clinical or laboratory features of overlap syndromes and no clinically swollen joints, attending the scleroderma clinic, were screened for arthralgia. Of these patients, 20 reported arthralgia and were invited to participate in the study. Of these, 17 patients participated. The study was approved by the South Sefton Research Ethics Committee. All patients participating in the study provided written informed consent. At entry, all patients had detailed history and a full clinical assessment of the musculoskeletal system and skin for modified Rodnan skin score (mRSS). All patients had arthralgia, but none had any symptoms or signs of inflammatory arthritis. Age, sex, disease duration (since first non-Raynaud’s symptom), antibody profile and organ involvement were documented. MSUS evaluation was performed using a Xario (Toshiba Medical Systems Corporation, Tokyo, Japan) equipped with a broadband linear probe (7–14 MHz). A.C., a rheumatologist experienced in MSUS, sequentially performed scans of both wrists and hands assessing joints (radiocarpal, inter-carpal, MCP, PIP and DIP) and tendons (all extensor and flexors of the fingers at the level of the wrists) using a multiplanar and dynamic scanning technique according to standard ultrasonographic scans proposed by the EULAR Working Group for MSUS in Rheumatology [7]. All explored joints and tendons were evaluated for the presence of SF and synovial hypertrophy on grey scale and synovitis/tenosynovitis on power Doppler ultrasonography (PDUS) signal according to OMERACT definitions criteria [9]. The following values of Doppler settings were used: frequency 7.5 MHz, low wall filter, pulse repetition frequency ranging from 700 to 1000 Hz and the maximal gain level not generating artefacts signal below the bony cortex. The presence of synovitis/tenosynovitis on grey scale and PDUS signal suggested synovial inflammation on MSUS, as per previously published guidelines [10].

Thirteen unselected patients, of the initial 17, had a second MSUS of both hands after a 6-month interval performed by the same sonographist to look for persistence of synovial inflammation. Eight unselected patients (out the 13) also had MRI scan with i.v. gadolinium contrast of their most symptomatic hand and wrist, within the same week of having the second MSUS. (Of the five patients who did not have MRI, four patients had to be excluded due to claustrophobia, renal impairment and contrast allergies and one failed to attend her MRI appointment.) MRI was performed with a 3T magnet with a dedicated peripheral radiofrequency coil. Fast spin-echo PD-weighted, fat-suppressed, multislice images [repetition time (TR) = 2500, echo time (TE) = 33 ms, 2-mm slice thickness, 0.4-mm in-plane resolution] and pre- and post-contrast 3D volume interpolated breath hold examination (VIBE) images (TR = 8 ms, TE = 4 ms, flip angle = 30°, 0.5-mm isotropic resolution) were acquired. MRI images were independently assessed by three musculoskeletal radiologists (blinded to ultrasonographic findings), qualitatively for the presence of clinically significant synovitis, tenosynovitis, bone marrow oedema and erosions (excluding patterns consistent with degenerative change). Images were then scored using a semi-quantitative scoring system for synovitis, erosion and bone marrow oedema, used to score MRI scans in RA (RAMRIS) [11]. Serum was obtained for hsCRP. Non-parametric data were compared using two-sample Wilcoxon rank-sum (Mann–Whitney U-test) test.

Results

Patient demographics and disease characteristics
Fourteen (82%) patients had lcSSc and three (18%) had dcSSc, classified according to the extent of current skin involvement [8]. The median age was 58 (range 42–68) years for lcSSc and 53 (range 48–56) years for dcSSc. Among the 14 lcSSc patients, ANA was positive in 6 (43%), ACA in 5 (36%), anti-RNP antibody in 2 (14%) and anti-topo-I antibody in 2 (14%) patients (these two patients had current skin involvement of lcSSc but long-standing disease and organ involvement in the pattern of dcSSc). Among the three dcSSc patients, ANA was positive in one and anti-topo-I in one. The median mRSS was 4 (range 2–14) in lcSSc and 27 (range 6–38) in dcSSc out of a possible 51. All patients tested negative for RF.

US findings
MSUS identified inflammation (Fig. 1A and B) in a high proportion of patients: tenosynovitis was more common and seen in 8 (47%) of the 17 and 6 (46%) of the 13 patients at baseline and second MSUS, respectively, than synovitis, which was identified in 1 (6%) of the 17 and 3 (23%) of the 13 patients at baseline and second MSUS, respectively. There was 70% agreement for detection of synovial inflammation between baseline and second MSUS [expected agreement 50%, with a κ = 0.4 (P = 0.06)], suggesting that inflammatory joint disease and tendinopathy were persistent in many patients. MSUS failed to identify any erosion at either baseline or on second MSUS.

MRI findings
All eight patients showed evidence of synovial inflammation on MRI in the form of synovitis in 8 (100%) of the 8 and tenosynovitis in 7 (88%) of the 8 patients (Fig. 1C and D). Bone oedema was seen in 5 (63%) of the 8 and erosions in 6 (75%) of the 8 patients.

Comparison between MSUS and MRI
Table 1 shows comparison between MRI and MSUS in detecting synovitis, tenosynovitis and erosions.

RAMRIS scores
The RAMRIS score for synovitis was 12.6 (interquartile range (IQR) 8.6–16.7); for oedema was 3.4 (IQR 0.19–6.6) and for erosions was 9.75 (IQR 2.8–16.7).
Disease characteristics and synovial inflammation

Statistical comparison between hsCRP, mRSS and synovial inflammation on MRI was not possible as all eight patients had MRI synovial inflammation. No associations were identified between mRSS, hsCRP and US inflammation. RAMRIS scores did not correlate with any disease measures. Also, disease duration, subtype and antibody status did not have any significant relation to inflammation seen on MRI or MSUS.

Discussion

This study confirms MSUS and MRI evidence of an inflammatory arthropathy in a high proportion in this small group of SSc patients with arthralgia, without an overlap with RA. Furthermore, MRI confirms the erosive nature of this arthropathy. Also, to our knowledge, this is the first study comparing MSUS and MRI in their ability to characterize inflammatory arthritis in SSc patients.

Joint space narrowing, juxta-articular osteoporosis and erosions in hands and feet joints of SSc patients as seen on X-ray (with or without overlap syndrome), have been reported in the literature [2–3], but synovitis has been little studied.

In the 1960s, Rodnan [12] reported that SSc patients with definite and troublesome joint symptoms had inflammatory changes in the synovium on biopsies. In the 1970s, Schumacher [13] reported fibrin deposition and mild focal proliferation of synovial lining cells, with perivascular infiltration of lymphocytes and plasma cells in a proportion of SSc patients, further supporting evidence of

TABLE 1 Comparison between MSUS and MRI in the eight patients who underwent both examinations

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<th>Synovitis</th>
<th>Tenosynovitis</th>
<th>Erosion</th>
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<tbody>
<tr>
<td>MSUS (n = 8)</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>MRI (n = 8)</td>
<td>8</td>
<td>7</td>
<td>6</td>
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<td>Percentage of agreement</td>
<td>38</td>
<td>62</td>
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synovial inflammation. Moving on to the 1990s, thermography and isotope bone scanning were used to characterize the arthritis in a group of 34 SSc patients and identified synovitis in 88%, with a majority having lcSSc [14]. However, the authors report that in a subset of their patients with deforming arthritis in this study, 70% of patients also met the classification criteria for RA, raising the possibility of RA–SSc overlap.

Recently, mild inflammatory changes in the joints of SSc patients on MRI scan were reported by Boutry et al. [15]. In 2009, Low et al. [16] reported more florid inflammatory changes on MRI, in a significant proportion of their symptomatic SSc patients. However, their study cohort included patients with clinically swollen joints and positive serology for RF suggesting inclusion of patients with features of RA overlap. At the time of assessment, the exclusion of patients with positive RF serology and swollen joints allowed a reasonable assumption that our cohort did not include patients with clinically apparent RA overlap.

Although there are no previous reports using MSUS in this setting, this study suggests that MSUS detects synovial inflammation and confirms its persistent nature in these patients. MRI proved to be much more sensitive in detecting synovial inflammation and erosions than MSUS in our study. An additional advantage of MRI is that it can detect bone oedema, which may be an important predictor of musculoskeletal outcome in terms of damage, similar to that in RA.

The mean RAMRIS scores in this study fall within the range of scores obtained from early [17] and established [18] RA. This suggests that the extent of the synovitis, bone marrow oedema and erosions may not be dissimilar between RA and this cohort of SSc patients. Although small erosions can sometimes be observed in healthy individuals on MRI [19], erosions seen in early RA tend to be associated with bone oedema and synovitis [19, 20]. This more inflammatory pattern of MRI erosions was seen in this group, with erosions in all patients associated with synovitis and five of the six with bone marrow oedema.

Despite this, SSc patients do not develop radiographic changes and deformity at the same rate as that in RA. This difference could be because inflammation in SSc is usually low grade and is replaced by fibrosis at some stage, and also immune mechanisms different from RA may be involved. Further studies with a larger SSc cohort allowing age- and sex-matched comparison in RAMRIS scores between SSc and RA patients will explore this further.

Our study has a number of limitations. This is a small study and includes patients with lcSSc and dcSSc subtypes, with varied disease duration. Also, only symptomatic patients with arthralgia were included in the study (without a control group consisting of SSc patients without arthralgia), and hence the findings cannot be generalized to all SSc patients. Nevertheless, this cohort represents a true clinical subset of SSc patients without overt overlap syndromes, and underlines the importance of fully investigating the arthralgia of SSc. The fact that MRI showed synovitis in all patients, but MSUS did not, raises the possibility that MRI is oversensitive in detecting synovitis. However, these patients had symptomatic arthralgia, and it is possible that MRI may predict clinically relevant joint disease in this cohort. Not all joints are accessible for identifying erosions on a standard 2D MSUS and this may partly explain why MSUS failed to show the erosions identified on MRI.

We acknowledge that standardization for both MRI and MSUS was acquired from the nascent RA literature; nevertheless, there are no validation techniques looking at joint and tendon pathology with MRI and MSUS in SSc or other CTDs as this is a relatively novel area of interest.

Two of the study patients who showed significant synovitis/tenosynovitis on both MSUS and MRI were given local steroid injections with good symptom resolution supported by a marked improvement in power Doppler signal on MSUS performed 2 weeks later suggesting this may be an effective short-term treatment strategy in these patients. However, currently there is no evidence that supports this intervention in patients with SSc and it is not clear whether suppression of subclinical synovitis in SSc would result in improvements in more long-term outcomes.

This study adds to the body of accruing evidence that synovial inflammation is common and under-recognized in SSc. These results are hypothesis generating and further larger longitudinal studies stratifying MRI and MSUS inflammation according to SSc subtype and disease duration will enable us to understand the full significance of these findings in the context of SSc pathogenesis and allow development of systemic treatment strategies.

Rheumatology key messages

- SSc patients with arthralgia may have an erosive inflammatory arthritis.
- MRI is more sensitive than MSUS in characterizing synovial inflammation and identifying erosions.
- RAMRIS system normally used to score MRI in RA can be used to quantify the inflammatory arthritis seen in SSc.

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