Advanced MRI in inflammatory arthritis

van der Leij, C.

Chapter 5

Peripheral joint inflammation in early onset spondyloarthritis is not specifically related to enthesitis

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Abstract

Objectives
A pivotal MRI study of knee arthritis indicated that enthesitis was more frequently observed in established spondyloartritis (SpA) than rheumatoid arthritis (RA). Subsequent MRI and ultrasound studies, however, failed to consistently demonstrate primary synovitis in RA versus primary enthesitis in SpA. Therefore, the current study aimed to reassess enthesitis versus synovitis in peripheral arthritis by a combined imaging and histopathological study in early untreated disease.

Methods
MRI and mini-arthroscopic synovial biopsy sampling were performed in 41 patients with early untreated knee or ankle arthritis, who were diagnosed with SpA (n=13), RA (n=20) or crystal arthropathy (n=8) at follow-up. MRI evaluation of enthesitis and synovitis, and immunohistochemical characterisation of synovitis were performed by two observers blinded to diagnosis.

Results
MRI showed similar prevalence of perientheseal fluid/oedema (67% vs 75%), perientheseal bone marrow oedema (0% vs 10%) and entheseal enhancement (46% vs 47%) in SpA versus RA, respectively. The number and distribution of affected entheseal sites were not different between both diseases. The MRI synovitis score was significantly higher in SpA (median 1.4; IQR 1.1–1.5) compared with RA (median 0.5; IQR 0.0–1.3) (*P*=0.028). Synovial histopathology showed a numerical increase in infiltrating cells in SpA versus RA synovitis which reached significance for CD163 macrophages in the synovial sublining (*P*=0.030). There were no differences compared with the crystal arthropathy control group.

Conclusion
Enthesitis on MRI is not a specific feature of peripheral arthritis in recent onset SpA versus RA. Synovitis is prominent in both diseases as evaluated by MRI and immunohistochemistry.

Introduction

Differences in clinical pattern, synovial histopathology, structural damage and response to treatment indicate that peripheral arthritis in spondyloarthritis (SpA) is distinct from rheumatoid arthritis (RA). A pivotal hypothesis attempting to explain these differences proposed that in peripheral arthritis synovitis is the primary feature of RA, whereas enthesitis is the primary lesion in SpA.[1] This was based on a MRI study in 10 SpA and 10 patients with RA with recent onset knee effusion, which showed that entheseal abnormalities were prominent in SpA: all SpA but only four patients with RA had perientheseal fluid/oedema, and six SpA but no patients with RA had perientheseal bone marrow oedema.[2]

The value of this hypothesis is that it proposed a conceptual framework potentially explaining the tissue-specificity of SpA lesions and that it emphasised the role of mechanical stress in SpA.[1,3] However, this hypothesis also has important weaknesses. First, the original study was cross-sectional in established disease and did not include histopathology.[2] Therefore, one cannot conclude that enthesitis is 'primary' to synovitis in SpA. Second, other imaging studies attempting to reproduce these findings yielded conflicting results. Some studies confirmed the higher prevalence of enthesitis in SpA versus RA[4–8] but others did not find more enthesitis in SpA compared with other inflammatory joint diseases,[9–12] questioning the specificity of this finding for SpA. Third, studies of peripheral enthesitis in SpA-associated diseases such as psoriasis, inflammatory bowel disease and human leukocyte antigen (HLA)-B27 positive uveitis in patients without arthritic symptoms demonstrated more enthesitis in these patients compared with healthy or non-SpA associated controls,[13–20] but most studies only assessed subclinical enthesitis and not subclinical synovitis, making it impossible to conclude which relationship exists between enthesitis and synovitis in the state before onset of full-blown SpA. However, the studies which investigated subclinical enthesitis and subclinical synovitis, showed that both features were more often present in SpA-related diseases compared with controls.[13,14] Furthermore, since follow-up data is scarce, it is unknown whether these patients will really develop full-blown SpA over time. Fourth, animal models also yielded conflicting results. The ankylosing enthesitis model in DBA/1 mice demonstrates that entheseal stress can lead to osteoproliferation and mild inflammation,[21] reminiscent of heel enthesitis in human SpA. Enthesitis is, however, also observed in erosive polyarthritis of TNF-ΔARE mice.[22] Moreover, interleukin[23] overexpression can lead to primary synovitis[23] and enthesitis.[24] Of most relevance to human SpA, finally, spontaneous peripheral arthritis in human HLA-B27/β2 microglobulin transgenic rats is characterised by pronounced synovitis in the absence of enthesitis.[25]

Testing the validity of the proposed hypothesis[1] is of relevance for pathophysiological and clinical research. If the hypothesis is correct, pathophysiological studies should focus on experimental models of enthesitis rather than synovitis and translational research should aim to obtain and study human entheseal rather than synovial

biopsies. Similarly, clinical studies should focus on drugs and interventions targeting enthesitis rather than compounds with proven efficacy on synovitis. Therefore, this study aimed to further elucidate the share of enthesitis and synovitis in peripheral arthritis in early SpA by comparing the presence and extent of these features in early untreated SpA and RA by paired MRI and synovial histopathology.

Materials and methods

Study patients

Forty-one patients from our early arthritis cohort with less than 12 months disease duration and active knee (n=28) or ankle (n=13) arthritis were included.[26] None of the patients had received disease modifying antirheumatic drugs, corticosteroids or biological treatment before inclusion. At 2 year follow-up, patients were classified as SpA (n=13) according to the European Spondyloarthropathy Study Group (ESSG)[27] and the Assessment of SpondyloArthritis International Society (ASAS) criteria[28] or RA (n=20) according to the 1987 ACR[29] and 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria.[30,31] The remaining eight patients were diagnosed as crystal arthropathy (CA) based on crystals in their synovial fluid or chondrocalcinosis on x-ray. The characteristics of the patients are depicted in Table 5.1. The SpA group consisted of seven patients with undifferentiated spondyloarthritis, four patients with psoriatic arthritis (PsA) and two patients with reactive arthritis. In the RA group 13/20 patients were anticyclic citrullinated protein antibodies and/or IgM rheumatoid factor positive. Demographic and clinical data (patient's global assessment of disease activity, 66/68 swollen and tender joint count, C reactive protein and erythrocyte sedimentation rate) and MRI scans of an inflamed knee or ankle were obtained at baseline. Twenty-three patients (SpA=8, RA=10, CA=5) underwent paired mini-arthroscopic synovial biopsy sampling of the inflamed knee or ankle, as described previously.[32,33] All patients gave written informed consent to participate in the study as approved by the local ethics committee.

MRI acquisitions

Scans were made using a 1.5 T MRI Scanner (GE Signa Horizon Echospeed, LX9.0, General Electric Medical Systems, Milwaukee), in supine position with the knee or ankle placed in a dedicated extremity coil (Quadrature Detection) centrally in the magnetic field. A bolus of 0.1 mmol/kg Gd-DTPA contrast agent (Magnevist, Schering AG, Berlin) was given intravenously.

The knee joint protocol consisted of a sagittal short τ inversion recovery (STIR) (repetition time/echo time/inversion time 4000/73/170, slice thickness 4 mm, field of view 240 mm, matrix 256×192), sagittal T1-weighted spin echo (SE) (500/14, 4 mm, 240

mm, 256×224), and axial T2-weighted SE with fat saturation (FS) (4000/97, 4 mm, 200 mm, 256×224) before contrast, and sagittal T1-weighted SE and transversal T1-weighted SE FS (500/14, 4 mm, 200 mm, 256×224) after contrast. The ankle joint protocol consisted of a sagittal STIR (7300/70/170, 3 mm, 200 mm, 256×160), sagittal T1-weighted SE (600/14, 3 mm, 200 mm, 256×192), and axial T2-weighted SE FS (3800/95, 3 mm, 200 mm, 256×224) before contrast, and sagittal T1-weighted SE and axial T1-weighted SE FS (600/14, 3 mm, 200 mm, 256×224) after contrast.

Table 5.1 Clinical characteristics of study patients.

	SpA (n=13)	RA (n=20)	CA (n=8)
Male gender, n (%)	10 (77)	5 (25)	6 (75)
Age (years)	46 (32-51)	53 (39-57)	53 (48-61)
Disease duration (years)	0.2 (0.1-0.4)	0.1 (0.1-0.3)	0.2 (0.0-0.2)
BMI (kg/m2)	25 (22-27)	27 (23-32)	28 (23-34)
Patient's global assessment (0-100 mm VAS)	61 (29-82)	62 (36-78)	47 (20-77)
66 Swollen joint count	1 (1-4)	9 (4-14)	3 (1-4)
68 Tender joint count	6 (1-10)	16 (9-29)	2 (1-6)
CRP (mg/L)	14.9 (7.0-73.9)	12.4 (5.0-28.8)	3.0 (1.8-10.0)
ESR (mm/h)	30 (10-52)	27 (12-33)	10 (5-26)

Except where indicated otherwise, values are the median (interquartile range). SpA = spondyloarthritis; RA = rheumatoid arthritis; CA = crystal arthropathy; BMI = body mass index; VAS = visual analogue scale; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

MRI scoring

Enthesitis was assessed by the presence or absence of perientheseal fluid/oedema, and perientheseal bone marrow oedema on the T2-weighted and T1-weighted images, as described by McGonagle et al.,[2] and on STIR. Additionally, we assessed entheseal enhancement using precontrast and postcontrast T1-weighted images. The following entheseal regions of the knee were examined: quadriceps femoris tendon insertion, patellar ligament insertion on the patella and tibial tuberositas, iliotibial band insertion, lateral collateral ligament origo and insertion, lateral joint capsule origo and insertion, anterior cruciate ligament origo and insertion, posterior cruciate ligament origo and insertion, biceps femoris tendon insertion, semimembranosus tendon insertion, medial collateral ligament origo and insertion, posterior joint capsule origo and insertion. For the ankle the Achilles tendon insertion and plantar fascia insertion were assessed.

Synovitis was scored semiquantitatively on postcontrast sagittal T1-weighted images in four compartments of the knee (ranging from 0 to 3: no or minimal enhancing synovium (compared with healthy individuals) to large volume of enhancing synovial tissue). The lateral compartment was the space lateral from the patella below the suprapatellar bursa, the medial compartment the space medial from the patella below the suprapatellar bursa, and the central compartment the space behind the patella (containing the Hoffa's fat pad) and around the cruciate ligaments below the suprapatellar bursa. The suprapatellar compartment consisted of the suprapatellar bursa. For the knee synovitis score the mean was taken from the four compartments.

Concerning the ankles, synovitis was assessed similarly in the tibial/fibular/talar, talar/calcaneal, talar/navicular and calcaneal/cuboidal joint. For the ankle synovitis score the mean was taken from the four joints.
The scoring was done by two musculoskeletal radiologists (CvdL and MM), who were blinded to the patients' diagnoses.

Synovial immunohistochemistry

Synovial biopsy samples were snap-frozen in Tissue-Tek OCT (Miles, Elkhart, Indiana, USA) immediately after collection. Cryostat sections (5 µm) were cut and mounted on Star Frost adhesive glass slides (Knittelgläser, Braunschweig). Frozen sections were acetone fixed and stained with monoclonal antibodies directed towards T cells (CD3; UHT1, Dako, Glostrup, Denmark), B cells (CD22; RFB4; Chemicon, Billerica, Massachusetts, USA), macrophages (CD68; EBM-11, Dako), alternatively activated macrophages (CD163; 5cFAT, BMA Biomedicals, Augst, Switzerland) and endothelial cells (von Willebrand factor; F8/86, Dako). After rinsing, sections were sequentially incubated with a biotinylated secondary antibody, a streptavidin-horseradish peroxidise link, aminoethylcarbazole substrate as chromogen (all Dako) and haematoxylin as counterstain. As negative control parallel sections were incubated with isotype and concentration-matched monoclonal antibodies. All samples were stained in a single run to minimise technical biases, and subsequently scored semiquantitatively for cellular infiltration by two independent observers (NY and DB) who were blinded to the patients' diagnoses, as described previously.[34–37]

Statistical analysis

Data are presented as the median and IQR. Since our main question was to compare SpA to RA, Mann-Whitney U tests were used to compare these diseases. In case of differences, additional comparison to the control CA group was performed by Mann-Whitney U tests to assess whether SpA or RA was distinct form other types of arthritis. Categorical data were analysed using χ^2 tests. Correlation between enthesitis and synovitis parameters was assessed using Spearman's correlation tests. All statistical tests were two-sided. p Values less than 0.05 were considered statistically significant.

Results

Similar enthesitis frequency on MRI in SpA and RA peripheral arthritis

We first assessed the frequency of perientheseal abnormalities on knee and ankle MRIs during peripheral arthritis. Perientheseal fluid/oedema and entheseal enhancement occurred frequently, but perientheseal bone marrow oedema was rarely observed (Figure 5.1). In SpA 66.7% had perientheseal fluid/oedema, 0% perientheseal bone

marrow oedema and 45.5% entheseal enhancement, compared with 75%, 10% and 47.1%, respectively in RA (Table 5.2). Accordingly, the frequency of these lesions was not significantly different between early untreated SpA and RA. Also separate analysis of knee and ankle MR images failed to reveal differences (Table 5.2).

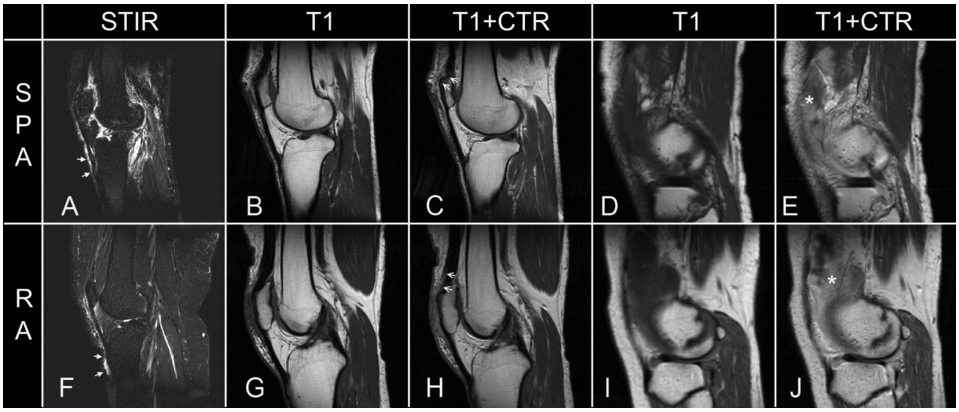

Figure 5.1 Representative magnetic resonance (MR) images of spondyloarthritis (A–E) and patients with rheumatoid arthritis (F–J). The MR images are sagittal short τ inversion recovery (STIR) images (A and F), sagittal T1 weighted images before (B, D, G and I) and after (C, E, H and J) contrast enhancement. A and F show perientheseal fluid/oedema at the patellar tendon insertion at the tibial tuberositas (closed arrows). C and H show subtle enhancement of the quadriceps tendon attachment (open arrows). E and J show extensive synovial hypertrophy and enhancement (*) in the lateral compartment of the knee.

Table 5.2 Frequency of enthesitis on MRI comparable between SpA and RA.

	Knee (n=28)			Ankle (n=13)			Knee and ankle (n=41)		
	SpA (n=8)	RA (n=13)	CA (n=7)	SpA (n=5)	RA (n=7)	CA (n=1)	SpA (n=13)	RA (n=20)	CA (n=8)
Peri-entheseal fluid/edema	5 (62.5)	9 (69.2)	7 (100)	3 (75.0)	6 (85.7)	1 (100)	8 (66.7)	15 (75.0)	8 (100)
Peri-entheseal bone marrow edema	0 (0.0)	2 (15.4)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	1 (14.3)
Entheseal enhancement	3 (42.9)	4 (36.4)	5 (71.4)	2 (50.0)	4 (66.7)	0 (0.0)	5 (45.5)	8 (47.1)	5 (62.5)

Values are the number (percentage) of patients with a positive finding on MRI. SpA = spondyloarthritis; RA = rheumatoid arthritis; CA = crystal arthropathy. The frequencies of enthesitis characteristics were comparable between SpA and RA and not different from CA. This was the case when knee and ankle were analyzed separately and when the data of knee and ankle were combined.

Similar extent and localisation of enthesitis on MRI in SpA and RA peripheral arthritis

As perientheseal abnormalities were frequently observed in peripheral arthritis independently of diagnosis, we next investigated whether the number or localisation of the enthesitis sites differed between SpA and RA. The median number of sites with perientheseal fluid/oedema per patient was 1.0 (IQR 0.0–2.0), perientheseal bone

marrow oedema 0.0 (IQR 0.0–0.0) and entheseal enhancement 0.0 (IQR 0.0–1.0) in SpA, and respectively 1.0 (IQR 0.0–2.8), 0.0 (IQR 0.0–0.0) and 0.0 (IQR 0.0–2.0) in RA (Figure 5.2). Accordingly, the number of entheseal sites with MRI abnormalities was not different between early SpA and RA peripheral arthritis, in the combined analysis of knees and ankles and in the separate analysis of these joints.

As to the localisation of the MRI abnormalities, perientheseal fluid/oedema and entheseal enhancement in the knee were most frequently seen at the patellar ligament insertion on the patella and tibial tuberositas, and the quadriceps femoris tendon insertion. In the ankle, these were mostly observed at the Achilles tendon and plantar fascia insertion. These localisations were similar in SpA and RA (data not shown). Perientheseal bone marrow oedema was only seen at the quadriceps femoris tendon insertion (two patients with RA) and patellar ligament insertion on the patella (one patient with CA). Taken together, these data indicate that MRI signs of enthesitis were not more predominant or differently distributed in SpA and RA early peripheral arthritis.

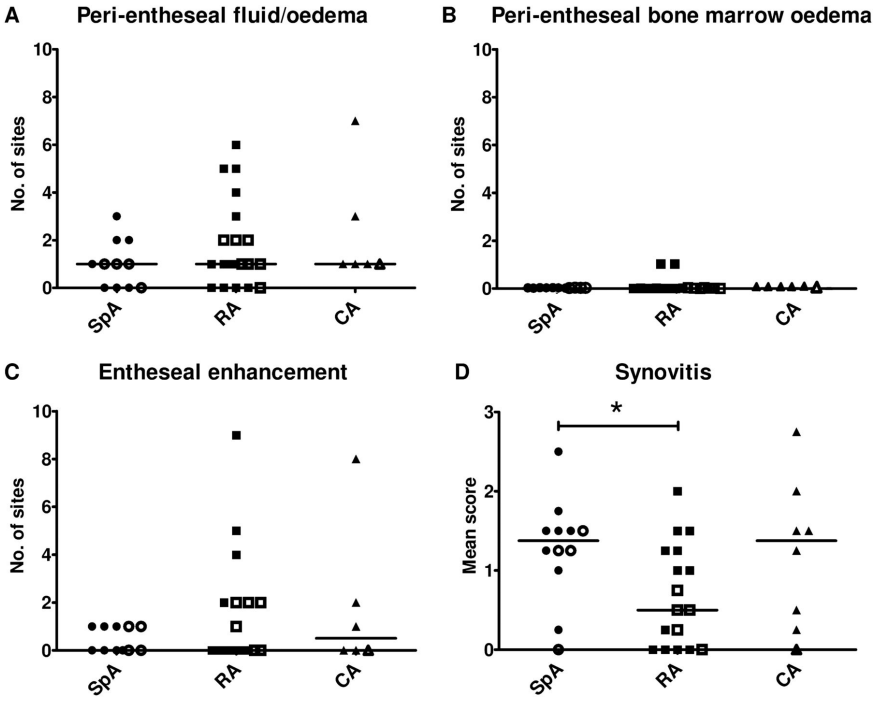

Figure 5.2 Enthesitis and synovitis assessed by Gd-DTPA enhanced magnetic resonance imaging (MRI) in patients with early spondyloarthritis (SpA), rheumatoid arthritis (RA) and crystal arthropathy. The panel represents the number of entheseal sites which show signs of enthesitis, assessed by three different enthesitis parameters: peri-entheseal fluid/edema (**A**), peri-entheseal bone marrow edema (**B**) and entheseal enhancement (**C**). The mean synovitis score is shown in figure **D**. The closed symbols represent the results for the knee MR images and the open symbols the results for the ankle MR images. * $P<0.05$ determined by Mann-Whitney U tests.

More pronounced MRI synovitis in SpA and RA peripheral arthritis

As synovitis has been proposed to be primary in RA but not SpA,[1] we additionally scored the degree of synovitis on MRI. The median synovitis scores were higher in SpA (1.4; IQR 1.1–1.5) than RA (0.5; IQR 0.0–1.3) (*P*=0.028) (Figure 5.2). There were no significant differences compared with CA. Also when the knee joints were analysed separately, the synovitis score tended to be higher in SpA (1.5; IQR 1.1–1.7) than RA (1.0; IQR 0.0–1.5) (*P*=0.087). For the ankle joints there was a similar numerical difference (1.3; IQR 0.3–1.4 in SpA vs 0.5; IQR 0.2–0.8 in RA) (*P*=0.198). In both diseases there was no correlation between the synovitis score and the number of affected entheseal sites in the knee or ankle (data not shown).

Similar degree of immunohistological synovitis in SpA and RA

In order to confirm the MRI findings indicating that synovitis was not more pronounced in RA than SpA early peripheral arthritis, we additionally assessed the severity of synovial inflammation by immunohistochemistry (Table 5.3). The number of infiltrating T cells (CD3), B cells (CD22) and macrophages (CD68) in the synovial lining and sublining was not different between SpA and RA. In line with previous findings, the number of CD163 macrophages was significantly increased in the synovial sublining of SpA (2.0; IQR 1.0–2.0) versus RA (1.0; IQR 0.8–1.3) (p=0.030).[34–37] The expression of von Willebrand factor (reflecting the degree of synovial vascularisation) was not different between SpA and RA.

As we previously reported that the degree of synovial sublining infiltration with CD68 macrophages accurately reflected disease activity in peripheral arthritis,[35,37] we confirmed the validity of our synovitis assessments by demonstrating a good correlation between the both MRI synovitis score and the CD68 sublining score (R=0.686) (*P*=0.001). Taken together, both MRI and immunohistochemistry showed that peripheral arthritis is characterised by pronounced synovitis in early SpA and RA.

Table 5.3 Synovitis assessed by immunohistochemistry.

Marker	SpA (n=8)	RA (n=10)	CA (n=5)	*P* SpA vs RA
CD3	1.5 (0.0-3.0)	0.5 (0.0-1.3)	0.5 (0.5-1.3)	0.2116
CD22	0.0 (0.0-1.3)	0.0 (0.0-0.6)	0.0 (0.0-0.75)	0.5363
CD68 lining	2.0 (1.0-2.5)	1.5 (1.0-1.9)	2.0 (1.0-2.8)	0.4850
CD68 sublining	2.0 (0.5-2.5)	0.8 (0.5-1.4)	1.5 (1.0-1.8)	0.2489
CD163 lining	1.0 (0.0-2.0)	1.0 (0.0-2.0)	1.0 (0.5-2.5)	0.7979
CD163 sublining	2.0 (1.0-2.0)	1.0 (0.8-1.3)	1.0 (1.0-2.0)	0.0304
von Willebrand Factor	2.0 (1.0-2.0)	1.5 (1.3-2.6)	1.5 (1.0-2.0)	0.9641

Values are the median (interquartile range). SpA = spondyloarthritis; RA = rheumatoid arthritis; CA = crystal arthropathy. Statistical analysis performed using Mann-Whitney U test. *P*<0.05 was considered statistically significant. There were also no significant differences compared to crystal arthropathy.

Discussion

This combined imaging and histopathological study assessed the presence and extent of enthesitis and synovitis in early untreated SpA versus RA peripheral arthritis. The major findings are that the frequency as well as the extent and localisation of enthesitis are similar in SpA and RA. Moreover, the degree of synovitis as assessed by MRI and immunohistology is similar or even slightly increased in SpA versus RA. These findings do not support the hypothesis that enthesitis would be primary and synovitis only secondary in SpA, compared with synovitis as primary lesion in RA.[1]

Several studies previously attempted to confirm the findings of the original MRI study by McGonagle et al.[2] with inconsistent results. Some reported increased frequency of enthesitis in SpA[4-8] whereas others did not find any differences between RA and SpA.[9-12] Interpretation of these data is complicated by the fact that these studies used different approaches (MRI, ultrasound, Power Doppler ultrasound) and enthesitis scores. This results in wide variability of findings with, for example, a reported frequency of enthesitis ranging from no enthesitis at all[6] 8 to 60% in RA.[4] To avoid potential biases, we based our approach on the study by McGonagle et al.,[2] focusing on the same patient groups and using globally the same MRI parameters. The differences between the original report[2] and the present study are that (a) we included more patients, (b) all patients had early untreated disease, (c) diagnosis was made prospectively at follow-up, (d) ankle MRIs were included beside knee MRIs and (e) we assessed synovial histopathology in parallel. Our SpA and RA cohorts were well-matched for systemic disease activity (C reactive protein, erythrocyte sedimentation rate and patient's global assessment) and body mass index. The latter is crucial as patients with PsA often have high body mass index[38] which may lead to mechanical enthesopathy and thereby bias the comparison with RA.

Besides demonstrating that there was no difference in enthesitis during peripheral joint inflammation in early SpA and RA, we additionally demonstrated that synovitis was equally present and, if anything, even more pronounced in early SpA than in RA. We and others have previously demonstrated manifest synovitis in established SpA peripheral arthritis.[34-36,39,40] We also demonstrated that the overall degree and specific features of synovitis, including mast cell infiltration and a disease-specific myogene signature, were similar in early and established SpA.[41-43] This is in agreement with the current study demonstrating, by MRI and immunohistology, pronounced synovitis in early SpA. Additionally, the synovitis and entheseal scores did not correlate in the present study, and previous studies indicated that not only subclinical enthesitis but also subclinical synovitis was frequently detected in SpA related diseases, even in the absence of clinical joint symptoms.[13,14] Taken together, these data plea against the hypothesis that enthesitis is the primary lesion in SpA and leads over time to secondary synovitis.[1]

Although our study strongly questions the role of enthesitis as the unifying and primary feature in SpA, the data should be interpreted carefully. First, we do not question that

clinical heel enthesitis is specific for SpA. Our study only assessed enthesitis in the context of peripheral arthritis and we did not study clinical enthesitis. Second, in line with the study of McGonagle et al.[2] we only assessed large joints of the lower extremities. Therefore we cannot formally exclude that the presence and/or potential role of enthesitis may be different in small joints. It has been reported that distal interphalangeal (DIP) involvement in PsA may relate to the anatomical 'enthesis-like' organisation of the nail bed.[44] However, similar observations were made in osteoarthritis.[44] Third, although we increased the patient number compared with the study by McGonagle et al.,[2] the study population remains relatively small. Despite this limitation, however, the current results show not even a trend towards more enthesitis in SpA versus RA. Therefore we do not think that increasing the patient number will change the current conclusions. Fourth, we did not assess axial involvement in SpA and can thus not exclude that enthesitis may play a more prominent role in axial than peripheral SpA. However, a study with sacroiliac joint MRIs found that the synovium and subchondral bone marrow were more frequently inflamed in early disease, while enthesitis was more common in advanced disease.[45] Also, a histopathological study of sacroiliac biopsies showed that synovitis and subchondral bone marrow changes were more predominant, while enthesitis was neither the earliest nor the principal pathological change.[46] This is in agreement with our observations in human HLA-B27/β2 microglobulin transgenic rats where spontaneous tail spondylitis was characterised by a pronounced inflammatory pannus in the absence of enthesitis.[25] Fifth, we only studied entheses by imaging. Ideally we would also include histopathology, however entheseal biopsies are difficult to obtain. Moreover, the studies which studied entheseal histopathology yielded conflicting results.[47,48] Finally, our data do not question that mechanical stress may lead to inflammation in SpA. In agreement with previous studies,[49] we found that the most frequently affected sites are entheses exposed to mechanical stress. However, this was the case in SpA, and in RA and CA. Perientheseal abnormalities at these sites are also often found in osteoarthritis and even healthy individuals.[9,10,50] In line with animal data,[21] these data indicate that mechanical stress can induce entheseal changes and inflammation. To what extent this process in SpA is restricted to the entheses versus other stromal tissues such as synovium or bone, remains to be established in future studies.

In conclusion, enthesitis and synovitis are important pathological features of early SpA peripheral arthritis. However, enthesitis is not more prevalent or pronounced, and synovitis not less frequent or severe in early SpA versus early RA. These data challenge the hypothesis that enthesitis is the primary immunopathological lesion in SpA.

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