Characterisation of articular manifestations in primary Sjögren's syndrome: clinical and imaging features

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ABSTRACT

Objective. *Articular manifestations (AMs) are observed in a large proportion of patients with primary Sjögren's syndrome (pSS) and can occur at the time of pSS diagnosis or during the disease course. Although in the majority of cases AMs are mild and self-limiting, some patients may experience chronic polyarthritis requiring treatment with DMARDs. Ultrasonography (US) and magnetic resonance imaging (MRI) can help assessing the extent of articular involvement and guide the treatment. The aim of this study was to describe the clinical, serological, and histological picture of a cohort of pSS patients with AMs.*

Methods. *Clinical and serological records were retrospectively evaluated and either US or MRI were performed to evaluate AMs and their features were described according to the OMERACT scoring systems.*

Results. *One hundred and thirty-three pSS patients were enrolled, of whom 115 (86%) with articular involvement. In particular, 91 patients (68%) displayed AMs at the time of pSS diagnosis while 24 patients (32%) during the course of the disease. Patients with AMs during the disease course were diagnosed with pSS at a younger age and reported a higher VAS dryness compared to patients displaying AMs at pSS onset. Hands and wrists were the most frequently involved sites followed by knees, shoulders and ankles. Overall, a consistent number of abnormalities were detected, more by MRI than US. Hands and wrists were the most frequently evaluated sites and the prevalence of all MRI abnormalities was similar between the different sites and comparable between the groups.*

Conclusion. *pSS AMs encompass a wide disease spectrum ranging from arthralgia to erosive arthritis resembling RA and therefore represent an important determinant of patients' quality of life. Imaging techniques such as US and MRI may be useful in the follow-up of pSS patients for prompt identification of AMs, for the quantification of their extent and ultimately for providing guidance on treatment and improving patient care.*

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease specifically targeting exocrine glands and characterised by mucosal dryness in the majority of patients (1). However, general symptoms as fatigue, weight loss and fever, along with extraglandular manifestations involving lungs, kidneys, peripheral and central nervous system, skin and musculoskeletal system occur in at least one-third of patients, thereby increasing health care costs and affecting the quality of life (2, 3). The evolution into B-cell lymphoma represents one of the main causes of decreased survival in pSS and occurs in about 5% of patients (4). Articular manifestations (AMs), described for the first time in 1965 by Bloch and colleagues (5), are one of the most common types of extraglandular manifestations in pSS, with a frequency ranging from 25 to 98% (6). A great heterogeneity characterises AMs in pSS, that range from arthralgia to severe inflammatory arthropathy complicated by erosions. A systematic literature review performed by the EULAR-SS Task Force in 2015 found that joint involvement (including either arthralgia or arthritis) was reported in 2784 of 5268 (53%) patients, while arthritis was reported in 834 of 5276 (16%) patients (6) AMs seem to affect pSS patients regardless of gender, to involve small and large joints in similar proportions, with the more frequent pattern being an intermittent symmetrical non-erosive polyarthropathy (6, 7).

For a long time, erosive arthritis in pSS patients has been considered a rare condition, mostly identifying subjects with

coexistent rheumatoid arthritis (RA) (6). The introduction of more sensitive imaging techniques for the assessment of musculoskeletal complaints, such as ultrasonography (US) and magnetic resonance imaging (MRI), allowed the identification of erosive damage in up to 20% of pSS patients with AMs (8-14). AMs significantly influence the patients' quality of life, leading to disability and impaired function (15, 16), but unfortunately evidence on biomarkers able to predict which pSS patients will develop AMs and erosive complications are lacking.

B-lymphocyte hyperactivation is the most typical immunopathogenic abnormality of pSS, and accounts for the wide variety of circulating autoantibodies directed to circulating and tissue nuclear and/or cytoplasmic antigens. Moreover, the detection of novel autoantibodies in pSS has increased in the last years, showing a correlation with particular stages of the disease or clinical phenotypes, and predicting long-term complications such as lymphoma (17, 18). As far as AMs are concerned, data from the Big Data Sjögren Project Consortium showed that rheumatoid factor (RF)-positive patients had a higher mean ESSDAI score and a higher frequency of activity in the articular ESSDAI domain in comparison with RF-negative patients (19). On the contrary, the positivity of anti-CCP antibodies was found in 7.5–10% of pSS patients without any radiographic evidence of erosion (20), but their presence seems to be closely associated with synovitis (21). Conversely, no data are available with regard to antibodies against other citrullinated proteins (ACPA) and pSS-associated AMs.

This study aimed to describe the clinical, serological, and histological picture of a cohort of pSS patients with AMs, together with possible associations with ACPA specificities and imaging features.

Materials and methods

Population study and inclusion criteria

We conducted a retrospective study in two Tertiary Italian Rheumatology Units, from the University of L'Aquila and University of Perugia, respectively. All patients (≥18 years) fulfilled the 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome (22) and displayed AMs ascertained by clinical assessment and/or US or MRI during the follow-up. Arthralgia or synovitis due to other causes, such as osteoarthritis, infectious, metabolic, rheumatoid arthritis or other autoimmune diseases were excluded. We also excluded patients with SS associated with one or more systemic/organ-specific autoimmune diseases. Consecutive patients without AMs were included as disease controls. This study was conducted in compliance with the protocol of Good Clinical Practices and Declaration of Helsinki principles.

Data collection and serological assessment

The following data were recorded from the patients' medical charts, at the time of pSS diagnosis and first pSS-associated AMs: age, gender, the presence of ocular and oral subjective and objective symptoms, extra-articular pSS-manifestation, EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), clinical (clin) ESSDAI, EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), the Charlson comorbidity index, and focus score. Serological data included: complete blood cell count, C-reactive protein, complement fractions, anti-nuclear antibodies (ANA), anti-extractable nuclear antigens (anti-ENA) antibodies, RF, anti-cyclic citrullinated peptide antibodies (anti-CCP), cryoglobulins, gammaglobulins and monoclonal components. AMs included the number of tender and swollen peripheral joints, anatomical site of involved joints, type of involvement (symmetrical or asymmetrical), and presence and duration of morning stiffness. Articular examination was performed by expert Rheumatologists. Arthralgia was defined as joint pain without inflammatory signs in the joint involved; on the contrary, arthritis was defined as joint inflammation characterised by pain, heat, redness swelling and loss of function upon physical examination.

Patients undergoing imaging could either be prescribed US or MRI depending on the rheumatologist's judgement. The following US-findings were recorded from patients' medical charts, at the time of first pSS-associated AMs: synovitis/synovial hypertrophy/effusion/Doppler signal, tenosynovitis, erosion (23). With regard to MRI, the following findings were recorded from patients' medical charts, at the time of first pSS-associated AMs: bone erosions, osteitis/bone marrow oedema, synovitis, joint space narrowing, and tenosynovitis (24).

Serum samples were tested for different ACPA specificities with commercially available ELISA kits.

Statistical analysis

Data were analysed with STATA/SE 16.1. The Mann Whitney U-test, the Kruskall Wallis test and Dunn's test for pairwise multiple-comparisons were used as needed to compare continuous variables. Chi square was used for categorical variables. All tests were two tailed and values of $p<0.05$ were considered statistically significant.

Results

One hundred and thirty-three pSS patients were enrolled, of whom 115 (86%) experienced articular involvement; in particular, 91 patients (68%) displayed AMs at the time of pSS diagnosis while 24 patients (32%) during the course of the disease. Table I summarises the demographic, clinical, histological and serological features of patients at the time of pSS diagnosis, according to the presence (Groups 2 and 3) or absence (Group 1) of AMs and the timing of their appearance (Group 2: at pSS onset; Group 3: during pSS course). Patients in Group 3 were diagnosed with pSS at a younger age and reported a higher VAS dryness compared to Group 2. The significant difference of ESSDAI, namely higher values displayed at pSS onset by patients of Group 2, was due to the articular involvement at that time and in fact the difference was no longer significant if ESSDAI was calculated without the articular domain. As predictable, VAS pain was significantly

Table I. Demographic, clinical, serological and histological features at the time of pSS diagnosis of the overall pSS cohort and subgroups according to the presence/absence of AMs and timing of AM development.

	All		Group 1 No AMs		Group 2 AMs at pSS onset		Group 3 AMs in the course of pSS		*p*-value[1]
	n	%	n	%	n	%	n	%	
n.	133		18	14	91	68	24	18	
Female gender	117	88	14	78	80	88	23	96	ns
Xerostomia	117	88	15	83	79	87	23	96	ns
Xerophthalmia	120	90	14	78	82	90	24	100	ns
ESSDAI domains									
Constitutional	19	14	3	17	14	15	2	8	ns
Lymphadenopathy	31	23	7	39	17	19	7	29	ns
Glandular	20	15	1	6	12	13	7	29	ns
Articular	91	68	0	0	91	100	0	0	<0.0001
Cutaneous	15	11	3	17	9	10	3	13	ns
Pulmonary	17	13	5	28	11	12	1	4	ns
Renal	0	0	0	0	0	0	0	0	na
Muscular	1	1	0	0	0	0	1	4	ns
Peripheral nervous system	17	13	3	17	12	13	2	8	ns
Central nervous system	2	2	1	6	1	1	0	0	ns
Haematological	10	8	3	17	5	5	2	8	ns
Biological	56	42	9	50	35	38	12	50	ns
Lymphoma	2	2	1	6	0	0	1	4	ns
Fibromyalgia	23	17	2	11	14	15	7	29	ns
Reduced complement fractions	19	14	3	17	8	9	8	33	0.009
Reduced C3 only	14	74	1	25	5	63	8	100	
Reduced C4 only	0	0	0	0	0	0	0	0	
Reduced C3 and C4	5	26	2	75	3	37	0	0	
Hypergammaglobulinaemia	51	38	8	44	31	34	12	50	ns
Hypogammaglobulinaemia	7	5	0	0	4	4	3	13	ns
Monoclonal component	7	5	3	17	4	4	0	0	0.046
Cryoglobulinaemia	0	0	0	0	0	0	0	0	na
ANA	102	77	15	83	70	77	17	71	ns
Anti-ENA									ns
Neither anti-Ro nor anti-La	50	38	4	22	34	37	12	50	
Anti-Ro only	41	31	10	56	25	27	6	25	
Anti-La only	4	3	0	0	3	3	1	4	
Both anti-Ro and anti-La	38	29	4	22	29	32	5	21	
RF	52	39	7	39	38	42	7	29	ns
anti-CCP	0	0	0	0	0	0	0	0	na
Increased CRP	48	36	5	28	42	46	1	4	<0.0001
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	***p*-value[2]**
Age	52.8	12.6	54.1	16.0	53.6*	11.7	48.8	12.8	0.0003
VAS pain	5.3	3.2	2.4#	2.9	6.0	3.0	4.8	2.9	<0.0001
VAS fatigue	5.8	2.8	4.8	2.9	6.1	2.8	5.5	2.5	ns
VAS dryness	6.1	2.7	4.6§	2.3	6.2	2.8	6.8	2.1	0.03
ESSPRI	5.7	2.3	3.9#*	1.9	6.1	2.3	5.7	1.9	0.002
ESSDAI	7.6	6.3	8.9	9.7	8.0*	5.7	5.0	4.6	0.049
ClinESSDAI	7.3	6.3	8.4	9.6	7.9*	5.6	4.3	4.7	0.010
ESSDAI without articular domain	5.2	0.5	8.9	9.7	4.6	5.6	5.0	4.6	ns
Focus score	2.3	1.6	2.9	2.4	2.3	1.6	2.0	1.1	ns
Charlson comorbidity index	2.2	1.6	3.1	3.1	2.1	1.3	1.7	1.0	ns

[1]*p*-values obtained with the Chi square test. [2]*p*-values obtained with the Kruskall Wallis test. The other *p*-values (*$p<0.05$ *vs*. group 3; #$p<0.05$ *vs*. group 2; §$p<0.05$ *vs*. group 3) indicate pairwise multiple-comparisons performed with the Dunn's test.
pSS: primary Sjögren's syndrome; AMs: articular manifestations; ANA: anti-nuclear antibodies; ENA: extractable nuclear antibodies; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; CRP: C-reactive protein; VAS: visual analogue scale; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; clinESSDAI: clinical ESSDAI; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; ns: not significant; na: not applicable; SD: standard deviation.

lower in Group 1 compared to Group 2 but interestingly it did not significantly differ when comparing Groups 2 and 3. CRP was more frequently abnormal in patients already displaying AMs at diagnosis. Of interest, patients of Group 1 displayed more frequently reduced complement fractions and a monoclonal component compared to Groups 2 and 3. Neither anti-CCP antibodies nor any other ACPA specificity was detectable in the serum samples.

Table II shows a comparison between patients with (Group 2) and without (Group 1 and Group 3 cumulated) AMs at pSS diagnosis and similar differences as those highlighted in table 1 were observed. Table III displays the

Table II. Demographic, clinical, serological and histological features of pSS patients displaying or not AMs at pSS diagnosis.

	Group 2 AMs at pSS onset (n=91)		Group 1 and Group 3 No AMs at pSS onset (n=42)		*p*-value[1]
	n	%	n	%	
Female gender	80	88	37	88	ns
Xerostomia	79	87	38	90	ns
Xerophthalmia	82	90	38	90	ns
ESSDAI domains					
Constitutional	14	15	5	12	ns
Lymphadenopathy	17	19	14	33	ns
Glandular	12	13	8	19	ns
Articular	90	99	0	0	<0.0001
Cutaneous	9	10	6	14	ns
Pulmonary	11	12	6	14	ns
Renal	0	0	0	0	
Muscular	0	0	1	2	ns
Peripheral nervous system	12	13	5	12	ns
Central nervous system	1	1	1	2	ns
Haematological	5	5	5	12	ns
Biological	35	38	21	50	ns
Lymphoma	0	0	2	5	ns
Fibromyalgia	14	15	9	21	ns
Reduced complement fractions	8	9	11	26	0.014
Reduced C3 only	5	63	9	21	
Reduced C4 only	0	0	0	0	
Reduced C3 and C4	3	37	2	5	
Hypergammaglobulinaemia	31	34	20	48	ns
Hypogammaglobulinaemia	4	4	3	7	ns
Cryoglobulinaemia	0	0	0	0	0
Monoclonal component	4	4	3	7	ns
ANA	70	77	32	76	ns
Anti-ENA					
Neither anti-Ro nor anti-La	34	37	16	38	ns
Anti-Ro only	25	27	16	38	
Anti-La only	3	3	1	2	
Both anti-Ro and anti-La	29	32	9	21	
RF	38	42	14	33	ns
anti-CCP	0	0	0	0	
Increased CRP	42	46	7	17	0.0010
	Mean	**SD**	**Mean**	**SD**	***p*-value[2]**
Age	53.6	11.7	51.0	14.3	ns
VAS pain	6	3	3.7	3.1	0.0002
VAS fatigue	6.1	2.8	5.2	2.6	ns
VAS dryness	6.2	2.8	5.9	2.4	ns
ESSPRI	6.1	2.3	4.9	2.1	0.0138
ESSDAI	8	5.7	6.7	7.4	0.0319
ClinESSDAI	7.9	5.6	6.0	7.4	0.0078
ESSDAI without articular domain	4.6	5.6	6.7	7.4	ns
Focus score	2.3	1.6	1.7	2.9	ns
Charlson comorbidity index	2.1	1.3	2.3	2.2	ns

[1]*p*-values obtained with the Chi square test. [2]*p* values obtained with the Mann Whitney U-test.
pSS: Primary Sjögren's syndrome; AMs: articular manifestations; ANA: anti-nuclear antibodies; ENA: extractable nuclear antibodies; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; CRP: C-reactive protein; VAS: visual analogue scale; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; clinESSDAI: clinical ESSDAI; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; ns: not significant; na: not applicable; SD: standard deviation.

demographic, clinical and serological characteristics of pSS patients at the onset of the first pSS-associated AMs, which for Group 2 coincides with pSS diagnosis while for Group 3 was at an average of 6 years after pSS diagnosis. As expected, patients with AMs displayed a higher VAS pain compared to patients without AMs but, interestingly, they also displayed a higher VAS dryness resulting in a significantly higher ESSPRI. The VAS dryness was not related to the timing of AMs onset since it was similar between Groups 2 and 3. To note, despite a higher mean number of joints involved in patients of Group 2, the VAS pain was significantly higher in Group 3. Hands and wrists were the most frequently involved sites (Group 2: hand 70% of patients; wrist 71% of patients; Group 3 hand 71% of patients; wrist 71% of patients) followed by knees, shoulders and ankles. Although slight differences were present, statistical significance was not reached for involvement of any site, prevalence of clinically evident arthritis *versus* arthralgia nor symmetric *versus* asymmetric involvement. With regard to the latter, however, an important observation was that patients with a symmetric involvement (N=66/115, 57%) had a significantly lower time between pSS diagnosis and onset of the first pSS-associated AMs (years, mean ±standard deviation 0.56±2) compared to those with asymmetrical involvement (n=49/115, 43%; years, mean ±standard deviation 2.4±4.9; p=0.04). As far as imaging is concerned, a total of 220 sites were assessed, 109 by US and 111 by MRI (Tables IV and V). Overall, a consistent number of abnormalities were detected and the prevalence of abnormalities detected by MRI (range 14–66%) was higher than those detected by US (range 8–29%). Hands and wrists were the most frequently evaluated sites hence a more detailed evaluation was performed. As depicted in Table VI, the prevalence of all MRI abnormalities was similar between the different sites and comparable between Group 2 and 3. The low prevalence of US abnormalities detected did not allow further analysis by Group and site.

Discussion

To the best of our knowledge, this study was the first specifically designed to evaluate the clinical, histological and serological picture along with the role of imaging and ACPA specificities in pSS-associated AMs. Our results confirm the relevance of AMs in pSS and the high prevalence of RA-like features, namely synovitis, erosions and bone

Table III. Demographic, clinical, and serological features of pSS patients at the time of AMs diagnosis compared to pSS patients without AMs at the end of follow up.

Features at onset of AMs	Group 1 No AMs (n=18)		Group 2 and Group 3 AMs (n=115)		*p*-value[1]	Group 2 AMs at baseline (n=91)		Group 3 AMs in the course of the disease (n=24)		*p*-value[1]
	n	%	n	%		n	%	n	%	
ESSDAI domains										
Constitutional	3	17	16	14	ns	14	15	2	8	0.040
Lymphadenopathy	7	39	24	21	ns	17	19	7	29	ns
Glandular	1	6	19	17	ns	12	13	7	29	ns
Articular	0	0	115	100	<0.0001	91	100	24	100	ns
Cutaneous	3	17	12	10	ns	9	10	3	13	ns
Pulmonary	5	28	12	10	ns	11	12	1	4	ns
Renal	0	0	0	0	na	0	0	0	0	na
Muscular	0	0	1	1	ns	0	0	1	4	ns
Peripheral nervous system	3	17	14	12	ns	12	13	2	8	ns
Central nervous system	1	6	1	1	ns	1	1	0	0	ns
Haematological	3	17	7	6	ns	5	5	2	8	ns
Biological	9	50	47	41	ns	35	38	12	50	ns
Increased CRP	6	33	43	37	ns	36	40	7	29	ns
Site										
Hand	0	0	81	70	na	64	70	17	71	ns
Wrist	0	0	82	71	na	65	71	17	71	ns
Elbow	0	0	7	6	na	6	7	1	4	ns
Shoulder	0	0	25	22	na	22	24	3	13	ns
Hip	0	0	7	6	na	7	8	0	0	ns
Knee	0	0	30	26	na	27	30	3	13	ns
Ankle	0	0	23	20	na	20	22	3	13	ns
Foot	0	0	17	15	na	14	15	3	13	ns
Symmetrical involvement	0	0	66	57	na	56	62	10	42	ns
Clinically evident arthritis	0	0	45	39	na	35	38	10	42	ns
	Mean	**SD**	**Mean**	**SD**	***p*-value[2]**	**Mean**	**SD**	**Mean**	**SD**	***p*-value[2]**
Age at pSS diagnosis	54.1	16.0	52.6	12.1	ns	53.6	11.7	48.8	12.8	ns
Age at diagnosis of articular manifestations	na	na	54	11.7	na	53.6	11.7	55	11.3	ns
Years from pSS diagnosis	na	na	1.3	3.6	na	0	0	6.3	5.7	<0.0001
VAS pain	2.4	2.9	6.4	2.9	< 0.0001	6.0	3.0	7.9	2.1	0.009
VAS fatigue	4.8	2.9	6.3	2.8	ns	6.1	2.8	7.1	2.6	ns
VAS dryness	4.6	2.3	6.2	2.7	0.023	6.2	2.8	6.5	2.1	ns
ESSPRI	3.9	1.9	6.3	2.2	< 0.0001	6.1	2.3	7.1	1.6	ns
ESSDAI	8.9	9.7	7.9	5.3	ns	8.0	5.7	7.6	3.5	ns
ClinESSDAI	8.4	9.6	7.7	5.2	ns	7.9	5.6	7.3	3.5	ns
Charlson comorbidity index	3.1	3.1	1.9	2.3	ns	2.1	1.3	2.1	1.1	ns
Number of joints affected	na	na	na	na	na	7.7	5.1	4.4	2.3	0.022

[1]*p*-values obtained with the Chi square test. [2]*p* values obtained with the Mann Whitney U-test.
pSS: primary Sjögren's syndrome; AMs: articular manifestations; CRP: C-reactive protein; VAS: visual analogue scale; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; clinESSDAI: clinical ESSDAI; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; ns: not significant; na: not applicable; SD: standard deviation.

marrow oedema at MRI evaluation. An oligo-polyarticular arthropathy affecting in particular small joints (wrist and hand), is the most frequent articular picture observed in our cohort. Patients with a symmetric involvement had a significantly shorter time between pSS diagnosis and onset of the first pSS-associated AMs. Patients with AMs displayed a higher VAS pain and a higher VAS dryness compared to patients without AMs, resulting in a significantly higher ESSPRI. AMs seemed not to be associated with a B-cell chronic activation nor with systemic manifestations, except for a higher prevalence of CRP above the upper limit, when compared with patients without AMs, that display more frequently reduced complement fractions and a monoclonal component. AMs represent one of the most common manifestations in patients with pSS (6) but the wide range of reported prevalence in pSS is due, at least in part, to differences in the selection of patients according to various pSS criteria, the presence of overlapping diseases (*e.g.* RA, SLE), the variety of definition of joint involvement, and the use of different imaging techniques. Furthermore, as demonstrated in large patient cohorts, the systemic phenotype of pSS is strongly influenced by factors such as age, gender, ethnicity and place of residence, which are key geo-epidemiological players in driving the expression of systemic disease at diagnosis. For example, a recent study reported that Black/African American patients show

Table IV. Magnetic resonance imaging (MRI) features of sites involved in pSS patients.

	All sites (n=111)		Hand (n=40)		Wrist (n=50)		Elbow (n=3)		Hip (n=2)		Knee (n=10)		Ankle (n=4)		Foot (n=2)	
MRI features	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Synovitis	73	66	27	68	35	70	1	33	2	100	3	30	3	75	2	100
Joint effusion	69	62	26	65	30	60	1	33	2	100	7	70	2	50	1	50
Bone erosion	45	41	17	43	25	50	0	0	0	0	0	0	2	50	1	50
Osteitis/BME	34	31	10	25	15	30	0	0	2	100	3	30	3	75	1	50
Joint space narrowing	60	54	22	55	26	52	0	0	0	0	7	70	3	75	2	100
Tenosynovitis	15	14	3	8	4	8	3	100	0	0	1	10	3	75	1	50

BME: bone marrow oedema.

Table V. Ultrasonography (US) features of sites involved in pSS patients.

	All sites (n=109)		Hand (n=43)		Wrist (n=45)		Elbow (n=1)		Shoulder (n=3)		Knee (n=5)		Ankle (n=8)		Foot (n=4)	
US features	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Synovitis	29	27	7	16	9	20	1	100	3	100	5	100	2	25	2	50
Joint effusion	29	27	7	16	9	20	1	100	3	100	5	100	2	25	2	50
Synovial hypertrophy	11	10	2	5	4	9	0	0	3	100	0	0	2	25	0	0
Power Doppler signal	8	7	2	5	4	9	0	0	0	0	0	0	2	25	0	0
Tenosynovitis	18	17	7	16	4	9	1	100	0	0	0	0	4	50	2	50
Bone erosion	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table VI. Comparison of magnetic resonance imaging features of most frequently involved sites (hand and wrist) according to the timing of AMs onset.

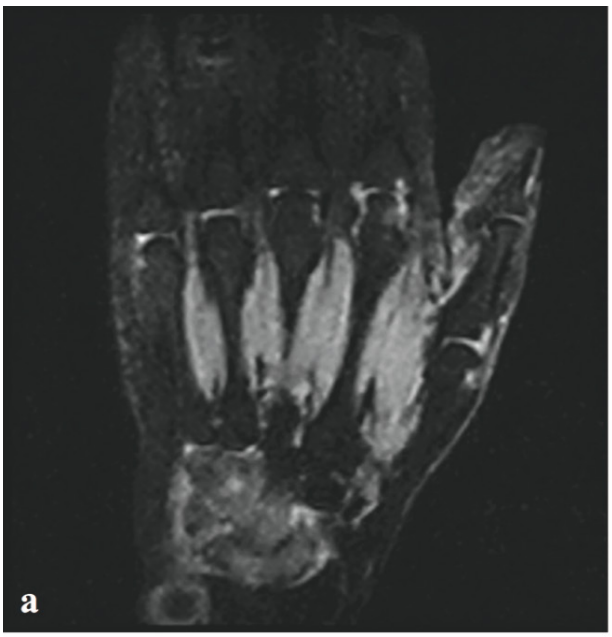
	Group 2 AMs at baseline		Group 3 AMs in the course of the disease		*p*-value
	Hand (n=29)	Wrist (n=36)	Hand (n=11)	Wrist (n=14)	
Synovitis	20 (69)	26 (72)	7 (64)	9 (64)	ns
Joint effusion	19 (65)	21 (58)	7 (64)	9 (64)	ns
Bone erosion	14 (48)	19 (53)	3 (27)	6 (43)	ns
Osteitis/BME	8 (27)	12 (33)	2 (18)	3 (21)	ns
JSN	14 (48)	19 (53)	8 (72)	7 (50)	ns
Tenosynovitis	2 (7)	2 (5)	1 (9)	2 (14)	ns

All values are indicated as number (percentage). n: indicates the number of sites.
More sites may have been assessed in the same patient. *p*-values were obtained with the Chi square test.
AMs: articular manifestations; BME: bone marrow oedema; JSN: joint space narrowing.

the highest frequencies in the articular ESSDAI domain (25). The articular ESSDAI domain identifies low, moderate and high activity level (22). However, the evaluation of arthralgia accompanied by morning stiffness (>30 minis) is limited to hands, wrists, ankles and feet, while the evaluation of synovitis is based on the 28 joint count used for the disease activity score (DAS)-28 (26). Nonetheless, our results demonstrated that AMs in pSS may affect different sites, also those not included in the articular domain of the ESSDAI, and any of them can display MRI abnormalities. Hence, ESSDAI may not capture the overall spectrum of AMs in pSS and it may be useful to include also number and location of involved joints and the AM pattern (symmetrical or asymmetrical). Furthermore, it may be advisable to specify which imaging technique should be used as reference, namely x-ray, US or MRI.

Over the last few decades, the increasing interest and consequent implementation in rheumatology practice of musculoskeletal (MSK) US and MRI, enriched the clinical assessment of patients with rheumatic and musculoskeletal diseases (RMDs). In this context, US and MRI may represent useful imaging techniques to elucidate the nature and extent of articular involvement in RMD, including pSS (Fig. 1). The concept that erosive structural damage is rare in RMDs other than RA has been challenged in the last few decades by the advent of these advanced imaging techniques. Our study confirmed that articular involvement in pSS may be of erosive nature in a subset of patients, although its distinguishing features remain controversial. Moreover, in pSS, whether the synovial membrane is the target of inflammation or erosions rather result from activation of other mechanisms remains to be elucidated.

Several studies demonstrated that musculoskeletal US is useful for detecting clinical and subclinical synovitis, tenosynovitis and erosions in pSS patients, with a frequency around 20–30%, according to different cohorts (9-14). On the contrary, conclusive data on the use of MRI in adult patients with pSS-associated AMs are lacking (8, 27). We observed a relevant proportion of MRI abnormalities in pSS patients with AMs regardless of the site and the timing of onset (at pSS diagnosis or during the course of the disease). Surprisingly, no erosions were detected by US but this can be explained at least in part by the fact that US is an operator and machine-dependent technique and that it is less sensitive than MRI. Although MRI is more expensive than US, the advantage of performing it may rely on



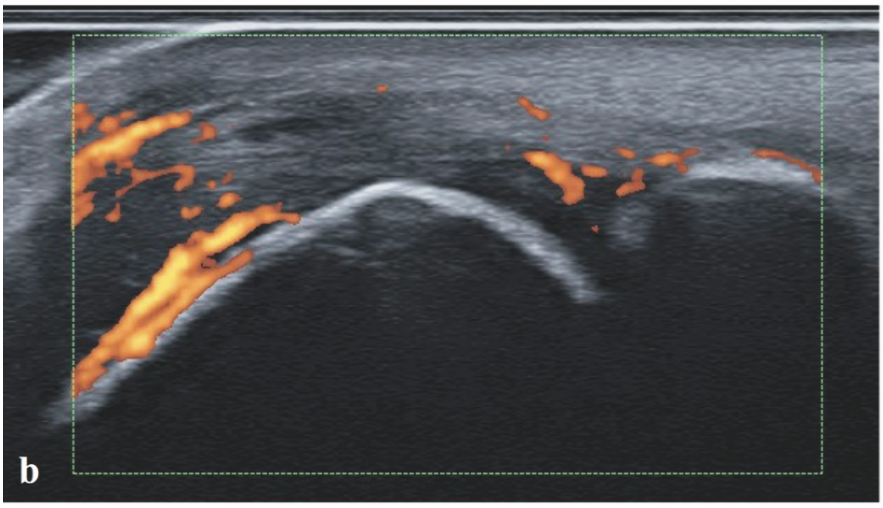


Fig. 1. a. Left hand and wrist magnetic resonance imaging scan (gradient echo STIR). The picture shows widespread morphological abnormalities with hyperplastic synovitis and reactive oedema of the carpal structures together with hyperplastic synovitis and erosions of the II-V metacarpophalangeal joints.
b. Ultrasonography image of third left metacarpophalangeal joint showing joint capsule distension and power Doppler signal within the joint cavity consistent with active articular inflammation.

its higher sensitivity, less operator-dependence and good safety profile since like US it does not expose patients to ionising radiations. Furthermore, it may also be helpful to overcome the lack of US facility in rheumatology clinics or the lack of US-trained rheumatologists in some centres.

As far as serology is concerned, the positivity of anti-CCP antibodies has been described in 7.5–10% of pSS patients without any radiographic evidence of erosion after a long follow-up (20, 28). However, in at least half of anti-CCP positive pSS, an evolution towards RA was often observed (29). In our study, none of the included patients displayed anti-CCP antibodies nor other ACPA specificities and at last follow-up point none of the patients displayed overt RA.

Unlike other RMDs such as RA and SLE, pSS is not characterised by a relapsing-remitting course but rather follows slowly progressive course, leading to cumulative tissue damage. On this basis, the clinical and immunological phenotype is almost fully blown at the time of pSS diagnosis (30). Although the presence of AMs at pSS diagnosis seems to predict a better outcome, in terms of disease activity after long-term follow-up (31), pSS-related AMs can emerge at any time of the disease course. Our results underscore the importance of a thorough follow-up of pSS patients, including frequent reassessment of clinical, biological and imaging parameters to ensure that the possible occurrence of erosive disease is promptly detected. Moreover, in our cohort not only VAS pain but also VAS dryness was higher in patients with AMs, resulting in a significantly higher ESSPRI. To note, VAS pain does not necessarily correlate with the number of involved joints but rather reflects the overall perception of patients. Therefore, although articular involvement may have a limited impact in the total ESSDAI value, it may significantly affect the patient quality of life and consequently patients' reported outcome, such as ESSPRI.

As far as the treatment of AMs is concerned, the recent EULAR recommendations for the management of SS with topical and systemic therapies (32) suggest the use non-steroidal anti-inflammatory drugs (NSAIDs) or hydroxychloroquine (HCQ) in patients with arthralgia, while NSAIDs, HCQ and low doses of corticosteroids (CS) or immunosuppressive agents in patients should be employed for arthritis. Synthetic immunosuppressive agents should be used mainly as CS-sparing agents, with no evidence supporting the choice of one agent over another, while the use of biological therapies, such as rituximab or abatacept, should be considered as rescue therapy. Although no studies focused on pSS-associated AMs, rituximab and abatacept could improve joint involvement (33, 34). It should be noted, however, that some patients developing AMs during the course of the disease were receiving HCQ, NSAIDs or CS so the use of these compounds for manifestations other than articular seems not to prevent the onset of AMs.

Our study has several limitations which could limit definitive conclusions, including its retrospective nature, the absence of a longitudinal follow up to determine whether patients with pSS and erosions could have later developed unequivocal RA, the fact that a dichotomous (presence/absence) descriptive report of US and MRI findings was used instead of a true morphometric assessment and that none of the sites was simoultaneously assessed by both US and MRI. Future studies should characterise in more detail pSS-associated erosive

arthritis and possibly also inflammatory involvement of other structures such as tendons in pSS.

In conclusion, pSS AMs encompass a wide disease spectrum ranging from arthralgia to erosive arthritis resembling RA and therefore represent an important determinant of patients' quality of life. Imaging techniques such as US and MRI may be useful in the follow-up of pSS patients for prompt identification of AMs, for the quantification of their extent and ultimately for providing guidance on treatment and improving patient care.

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