

PAPER

Association of CXCL13 serum level and ultrasonographic findings of joints in patients with systemic lupus erythematosus and Jaccoud's arthropathy

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Objectives: The objective of this paper is to perform an ultrasonography (US) analysis of hands and wrists in two groups of patients with systemic lupus erythematosus (SLE), with and without Jaccoud's arthropathy, matched by age and disease duration and to correlate them with levels of CXCL13 clinical features, laboratory tests and disease activity score. **Methods:** Sixty-four patients with SLE were enrolled, 32 with and 32 without Jaccoud's arthropathy. Each patient underwent physical examination, laboratory tests (including CXCL13 by ELISA) and bilateral US. Synovial hypertrophy, tenosynovitis and erosions were evaluated according to a semiquantitative grading system with a 0–3 rating. US findings were correlated with serum levels of CXCL13, other serological parameters and disease activity index. **Results:** Synovitis was found in 25/64 patients (39%) and tenosynovitis in 14/64 (22%). These findings were more frequent in SLE patients with Jaccoud's arthropathy, particularly tenosynovitis ($p=0.002$) and synovitis ($p=0.01$). Median serum level of CXCL13 was 20.16 pg/ml in the whole population (23.21 pg/ml in the Jaccoud's arthropathy group and 11.48 pg/ml in the group without). There was an association between the presence of disease activity and high level of CXCL13 ($p=0.004$). However, no association was found between high levels of CXCL13 and "arthritis" in SLEDAI, swollen joints on physical examination or synovitis on US. **Conclusions:** US findings in joints of SLE patients with Jaccoud's arthropathy confirm that synovitis and tenosynovitis are common in these patients. In addition, serum level of CXCL13 is associated with disease activity in SLE but does not seem to be a biomarker for arthritis in these patients. *Lupus* (2018) 27, 939–946.

Key words: Systemic lupus erythematosus; Jaccoud's arthropathy; CXCL13; ultrasonography

Introduction

Joint involvement in systemic lupus erythematosus (SLE) is frequently observed and is one of the earliest manifestations of the disease, appearing as arthralgia or arthritis.^{1,2} About 5% of SLE patients can develop a deforming and nonerosive type of arthritis known as Jaccoud's arthropathy (JA). It was originally observed in patients with rheumatic

fever,³ but presently SLE is the main clinical entity associated with JA.⁴ JA occurs in the metacarpophalangeal (MCP) and interphalangeal joints, presenting with "swan neck" deformity and ulnar deviation as seen in rheumatoid arthritis (RA), which is characteristically "reversible."^{5–9}

Recently, new diagnostic imaging techniques, particularly ultrasonography (US), have been used in the management of SLE disease.^{10–12} Its low cost and absence of ionizing radiation render it a cost-effective procedure.¹³

In the last few years, efforts have been made to identify the factors that can contribute to the development of JA.^{14–17} Previous studies have shown conflicting results regarding the association of JA

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with the profile of autoantibodies. Thus, no serum marker has been developed for it yet.¹⁸ In several autoimmune disorders, including SLE, chemokines have been shown to orchestrate the migration of B and T cells to inflammatory sites. Recent experimental studies have claimed the potential therapeutic benefit of pharmacological chemokine and chemokine receptor blockade in SLE.^{19–21} The chemokine CXC ligand 13 protein (CXCL13), also known as B-cell-attracting chemokine-1 or B-lymphocyte chemo attractant, is a CXC subtype member of the chemokine superfamily. It is one of the most potent B-cell chemo attractants and is constitutively expressed in the B-cell follicles of secondary lymphoid organs.²² In RA, its serum level has been correlated with the presence and intensity of synovitis when evaluated by US.²³

The aim of this study is to evaluate the association of serum level of CXCL13 with US findings of joints and clinical features of joint inflammation in SLE patients with JA.

Methods

Population

A series of patients who were diagnosed with SLE based on the American College of Rheumatology criteria were included in this study.⁴ They were divided into two groups: (a) those with JA based on the preliminary criteria suggested by Santiago;²⁴ and (b) a comparison group (SLE without JA), matched by sex, age and disease duration.

The whole sample population underwent a clinical evaluation, interview, and physical examination. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K updated version),²⁵ not scoring the item “ocular involvement” as ophthalmological evaluation was not performed. Physical examination of hand and wrist joints was recorded as a swollen joint and tender joint in each patient.

The study was approved by the ethics research committee of our institution. An informed consent was obtained from every patient prior to enrollment in the study.

US protocol

On the same day of the clinical assessment, patients and controls underwent a US evaluation of both wrists and hands by two radiologists specializing in the musculoskeletal system with more than 10 years of experience. They used a Philips HD11

XE US System (Koninklijke, Philips N.V., Eindhoven, The Netherlands) with a linear probe operation between 10 and 14 MHz. The radiologists were blinded to clinical findings, and they performed US examinations independently. The inter-observer agreement was evaluated in 20% of participants.

According to the European League Against Rheumatism guidelines for musculoskeletal US in rheumatology,²⁶ a multiplanar scanning technique was used for obtaining US images in transverse and longitudinal planes of each point: wrist (dorsal side of radiocarpal and ulnocarpal joints), dorsal and volar sides of the second to fourth MCP joints and proximal interphalangeal (PIP) joints, as well as flexor and extensor tendons from the second to fourth fingers on both hands. These anatomical sites were chosen because they were pathologically representative sites in accordance with previous studies of SLE patients.²⁷

Synovial hypertrophy, bone erosion, and tenosynovitis were diagnosed using US according to the preliminary definitions provided by the Outcome Measures in Rheumatoid Arthritis Clinical Trials, a special interest group for musculoskeletal US in rheumatology.²⁸ A semiquantitative grading method (0 to 3) for scoring synovial hypertrophy, tenosynovitis and bone erosion was used.

Synovitis was defined as abnormal hypoechoic (relative to subdermal) intra-articular tissue that is non-displaceable and poorly compressible and may exhibit Doppler signal.

The degree of synovitis was classified as follows: grade 0 = no synovial thickening, grade 1 = minimal synovial thickening (filling the angle between the periarticular bones, without crossing the line connecting the tops of the bones), grade 2 = synovial thickening crossing the line connecting the tops of the periarticular bones but without extension along the bone diaphysis, and grade 3 = synovial thickening crossing the line connecting the tops of the periarticular bones with extension to at least one of the bone diaphysis. The degree of tenosynovitis was also graded from 0 to 3: grade 0 = no signs of tenosynovitis (diameter of synovial tendon sheath ≤ 0.3 mm, on the maximal diameter detectable in transverse view); grade 1 = mild tenosynovitis (diameter of the synovial tendon sheath ≤ 2 mm, on the maximal diameter detectable in transverse view); grade 2 = moderate tenosynovitis (diameter of the synovial tendon sheath ≤ 4 mm, on the maximal diameter detectable in transverse view); and grade 3 = severe tenosynovitis (synovial sheath of the tendon

diameter > 4 mm, on the maximal diameter detectable in transverse view).

Erosion was defined as an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes. The degree of erosion was graded on a scale of 0 to 3: grade 0 = regular bone surface; grade 1 = irregularity of the bone surface without formation of a defect seen in two planes; grade 2 = formation of a defect on the surface of the bone seen in two planes; and grade 3 = bone defect (creating extensive bone destruction). Erosion was evaluated only in hand joints.

Our study did not use Power Doppler associated with the B-mode analysis of the joints. This could be a limiting factor in synovitis and tenosynovitis detection, but a recent systematic review observed that Power Doppler has unknown significance as a marker of disease activity in SLE owing to the lack of standardization of its criteria of evaluation.²⁹ On the other hand other recent studies have shown that the use of Power Doppler could facilitate this identification in lupus patients.³⁰

Laboratory tests

A blood sample was collected from each patient at the time of clinical evaluation, and the samples were tested for different autoantibodies such as antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA), anti-Smith (anti-Sm), anti-SSA and anti-SSB.

CXCL13 measurement

Serum concentration of CXCL13 was quantified in both groups utilizing a commercially available enzyme-linked immunosorbent assay kit following the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA, catalog number DCX130). All samples were collected and stored at -20°C until further analysis, and the serum samples were tested in duplicates. The serum level of CXCL13 was evaluated as a numerical variable and then categorized into high and low levels based on the 50th percentile.

Statistical methods

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 20, Chicago, IL, USA). Data were described as mean and standard deviation (SD) or median and interquartile range (IQR). Differences between the two groups were tested by the unpaired Student's *t* test or Mann-Whitney *U* test, after testing the normality of the quantitative variables. The

Pearson's chi-square test or Fisher's exact test was used to compare categorical variables among the groups. Correlation between variables was tested by Pearson's test or Spearman test depending on the normality of the variables. As cited above, CXCL13 serum level was categorized as low or high based on the distribution of its median value (50th percentile). For all statistical tests, a *p* value < 0.05 was considered significant.

Results

Clinical and laboratory findings

A total of 64 SLE patients (all women) were included in this study, i.e. 32 with JA and 32 without JA, matched by age, disease duration and time of arthritis. The mean age was 46.3 years (± 12.3) in the JA group and 46.3 years (± 12.4) in the group without JA. The mean duration of the disease was 17.3 years (± 7.7) in the JA group and 17.1 years (± 8.1) in the group without JA. Clinical evaluation of the joints revealed 95 (10.6%) tender joints and 34 (3.8%) swollen joints with a predominance of changes in the JA group (*p* = 0.02). The joint deformities most commonly seen in JA group were "swan neck" (all patients) and "ulnar deviation" (seen in 70% of the patients).

The demographic data and other clinical features of the entire population are presented in Table 1. Discoid lesions and cytopenias were more common in the JA group. The medications most frequently used by the patients were corticosteroids (prednisone, dose range 5 to 20 mg/daily), hydroxychloroquine (dose 400 mg/d), methotrexate (dose range 5 to 15 mg/weekly) and azathioprine (dose range 75 to 150 mg/daily). However, except for the corticosteroid use, there was no difference in the proportion of patients using such medications in both groups; the mean dose of prednisone also showed no difference in both groups.

Regarding the frequency of antibodies, it was observed that anti-dsDNA and anti-Sm antibodies were more prevalent in the JA group (Table 2).

US findings of joints and tendons in SLE

The US findings showed that synovitis was found in 25/64 patients (39%), tenosynovitis in 14/64 (22%) and erosion in 2/64 (3.1%). All of these findings were more frequent in SLE patients with JA, particularly tenosynovitis (*p* = 0.002) and synovitis, which was observed mainly in MCP joints (*p* = 0.01).

Table 1 Demographic and clinical manifestations of the SLE population

Findings	SLE with JA N = 32	SLE without JA N = 32	p value
Age (years), (mean ± SD)	46.2 (±12.3)	46.3 (±12.4)	0.99
Disease duration (years), (mean ± SD)	17.3 (±7.7)	17.1 (±8.1)	0.92
Arthritis duration (years), (mean ± SD)	15.2 (±7.8)	14.8 (±8.7)	0.88
Malar rash, n (%)	21 (65.6)	21 (65.6)	1.00
Photosensitivity, n (%)	26 (81.3)	26 (81.3)	1.00
Discoid lesion, n (%)	4 (12.5)	11 (34.4)	0.03
Oral ulcers, n (%)	12 (37.5)	15 (46.9)	0.44
Pleuritis, n (%)	9 (28.1)	3 (9.4)	0.05
Pericarditis, n (%)	5 (15.6)	2 (6.3)	0.42
Any renal abnormality ^a , n (%)	13 (40.6)	11 (34.4)	0.60
Lymphopenia ^b , n (%)	9 (28.1)	2 (6.3)	0.02
Leukopenia ^c , n (%)	16 (50)	8 (25)	0.03
Psychosis, n (%)	3 (9.4)	1 (3.1)	0.61
Seizures, n (%)	4 (12.5)	2 (6.3)	0.67
Current medication			
Corticosteroid ^d , n (%)	18 (56.3)	9 (30)	0.037
Hydroxychloroquine ^e , n (%)	24 (75.0)	19 (63.3)	0.319
Azathioprine ^f , n (%)	3 (9.4)	4 (13.3)	0.703
Methotrexate ^g , n (%)	5 (15.6)	3 (10.0)	0.709

^aRenal abnormality = proteinuria > 1 g/24 hours or renal dysfunction (serum creatinine above normal range) not attributable to another cause. ^bLymphopenia: = lymphocytes <1500 cells on two occasions. ^cLeukopenia = leukocytes < 4000 cells on two occasions. ^dCorticosteroid dose range 5–20 mg/day. ^eHydroxychloroquine dose 400 mg/day; ^fAzathioprine dose range 75–150 mg/day. ^gMethotrexate dose range 5–15 mg/weekly.

SLE: systemic lupus erythematosus; JA: Jaccoud's arthropathy; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SD: standard deviation.

Table 2 Frequency of different autoantibodies in the two groups of the SLE population

	SLE with JA n/n total (%)	SLE without JA n/n total (%)	p value
Anti-dsDNA	25/32 (78.1)	12/26 (46.2)	0.012
Anti-Sm	11/31 (35.5)	3/25 (12)	0.044
Anti-RNP	11/28 (39.3)	6/21 (28.6)	0.43
Anti-SSB	06/29 (20.7)	4/23 (17.4)	1.00
Anti-SSA	12/31 (38.7)	7/24 (29.2)	0.46
ANA	32/32 (100)	26/27 (96.3)	0.45

SLE: systemic lupus erythematosus; Anti-dsDNA: anti-double-stranded DNA; Anti-Sm: anti-Smith; ANA: antinuclear antibodies; JA: Jaccoud's arthropathy.

In the JA group, synovitis was found in 16.1% of 448 evaluated joints and tenosynovitis in 37.5% of the total tendons evaluated (192). In the majority of the cases, US synovitis and tenosynovitis were minimal (grade 1). In SLE without JA, synovitis was found in 3.8% of 448 joints and 1.5% of tendons, all graded as minimal.

Erosion was seen in two patients with JA (total of six joints), one with eight years of disease and arthritis and another with 33 years of disease and arthritis.

Details of the ultrasonographic findings are presented in Table 3.

The interobserver concordance was determined in 12 patients (six from each group; 20% of the entire sample). Moderate to good concordance was found for semiquantitative measures of synovial hypertrophy ($k=0.833$), tenosynovitis ($k=0.667$) and erosion ($k=0.625$). Figure 1 illustrates the main US findings obtained from an SLE patient with classical JA.

Association of serum level of CXCL13 with clinical and US findings

The median serum level of CXCL13 was 20.16 pg/ml (IQR 8.24–50.42) in the whole population, 23.21 pg/ml in the JA group and 11.48 pg/ml in the group without JA ($p=0.08$). In five patients, the serum level of CXCL13 was below the detection sensitivity of the method, three without JA and two with JA. They were excluded from the analysis. When serum level of CXCL13 was categorized as low or high as previously mentioned (50th percentile), a significant difference was observed between the groups with and without JA ($p=0.027$) (Table 4).

Twenty-one patients (32.8%) were classified as having active disease, arbitrarily defined by SLEDAI ≥ 6 . The level of CXCL13 was found to be correlated positively with the SLEDAI score

Table 3 Ultrasonographic findings in joints of SLE patients

Findings	SLE with JA n% (n/n total)	SLE without JA n% (n/n total)	SLE total n% (n/n total)	p value
<i>Radiocarpal joints</i>				
Synovitis	31.3 (10/32)	28.2 (9/32)	28.2 (18/64)	0.78
Erosion	6.3 (2/32)	0 (0/32)	3.1 (2/64)	0.49
<i>Hand joints</i>				
Synovitis				
Second MCP	31.2 (10/32)	3.1 (1/32)	17.2 (11/64)	0.003
Third MCP	28.2 (9/32)	0 (0/32)	14 (9/64)	0.005
Fourth MCP	28.2 (9/32)	0 (0/32)	14 (9/64)	0.01
Second PIP	0 (0/32)	0 (0/32)	0 (0/64)	–
Third PIP	3.1 (1/32)	0 (0/32)	1.5 (1/64)	1.0
Fourth PIP	0 (0/32)	0 (0/32)	0 (0/64)	–
Erosion				
Second MCP	6.2 (2/32)	0 (0/32)	3.1 (2/64)	1.0
Third MCP	6.2 (2/32)	0 (0/32)	3.1 (2/64)	0.35
Fourth MCP	0 (0/32)	0 (0/32)	0 (0/64)	–
Second, third and fourth PIP	0 (0/32)	0 (0/32)	0 (0/64)	–
<i>Hand tenosynovitis</i>				
Flexor tendon of the second finger	34.4 (11/32)	6.3 (2/32)	20.3 (13/64)	0.003
Flexor tendon of the third finger	34.4 (11/32)	0 (0/32)	17.2 (11/64)	< 0.001
Flexor tendon of the fourth finger	31.3 (10/32)	0 (0/32)	17.2 (10/64)	0.001

SLE: systemic lupus erythematosus; JA: Jaccoud's arthropathy; MCP: metacarpo-phalangeal; PIP: proximal interphalangeal.

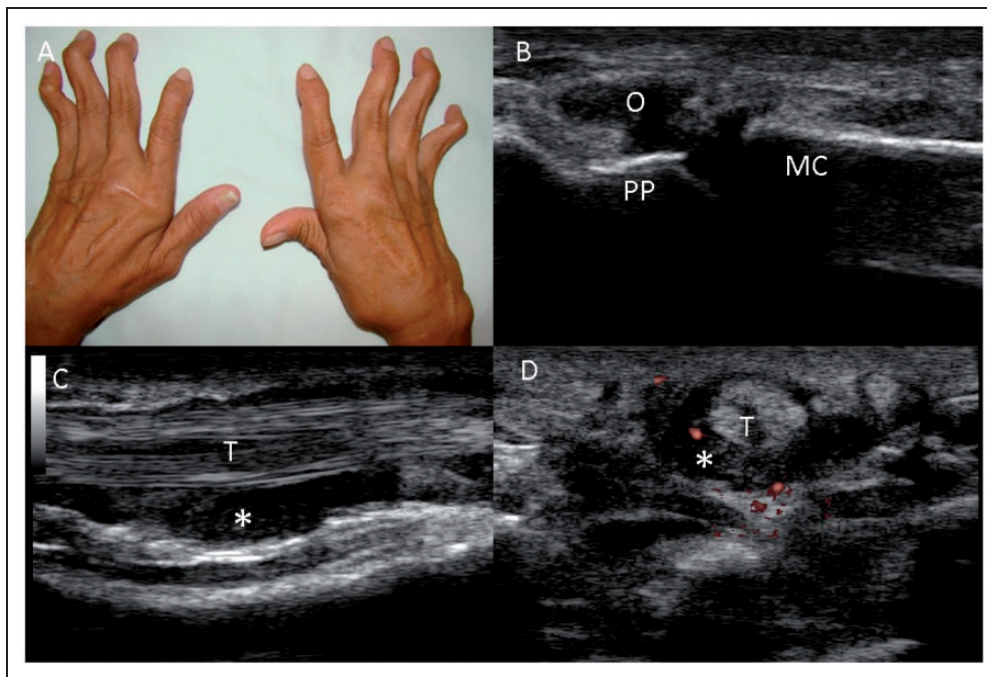


Figure 1 Typical Jaccoud's arthropathy joints in a 57-year-old woman with systemic lupus erythematosus of 26 years' duration (a); second metacarpophalangeal joint, longitudinal volar scan, showing effusion and synovial proliferation (b); tenosynovitis of the second flexor tendon in longitudinal (c) and transverse (d) scans. *Peritendinous effusion and synovial proliferation; T: flexor digitorum profundus tendon; O: effusion and synovial proliferation.

($R=0.33$; $p=0.01$). Although there was an association between the presence of elevated levels of CXCL13 (considering >50th percentile) and disease activity as a whole ($p<0.004$), it did

not occur with the item "arthritis" in SLEDAI score.

Regarding the US findings, there was an association between the presence of elevated serum levels

Table 4 Activity scores of SLE patients

Findings	SLE with JA N = 32	SLE without JA N = 32	p value
Whole SLEDAI score ≥ 6 , n (%)	15 (48.4)	5 (16.7)	0.008
Arthritis item in SLEDAI, n (%)	5 (16.1)	2 (6.7)	0.425
CXCL13 (median) (IQR)	23.2 (11.18–85.19)	11.5 (7.36–39.72)	0.08
Higher level of CXCL13 50th percentile n (%)	66.7	37.9	0.027

SLE: systemic lupus erythematosus; JA: Jaccoud's arthropathy; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; IQR: interquartile range.

of CXCL13 and tenosynovitis considering both groups altogether ($p = 0.024$). Such an association was not observed in the presence of synovitis and erosion.

Considering the physical examination, there was no association between the presence of swollen or tender joints and elevated levels of CXCL13. On the other hand, a positive association between swollen joints and synovitis ($p = 0.001$) or tenosynovitis (0.006) by US was found in the JA group. Also, in the same group, there was a positive association between painful joints and synovitis (0.008) but not with tenosynovitis (0.15).

Discussion

The etiopathogenic mechanisms of JA in SLE have not yet been clarified. Effort has been made to determine factors that can contribute to its development, and the search for novel biomarkers capable of predicting inflammatory joint processes seems to be a reasonable approach.

The present study is the first of its kind to provide data on the CXCL13 serologic level in comparison with US evaluation of musculoskeletal involvement in a large population of SLE with or without JA. A positive correlation between the level of CXCL13 and SLEDAI score in the entire studied population suggested that the expression of this chemokine could be associated with disease activity. Other studies have also observed the association between CXCL13 level and disease activity in SLE, for example, with lupus nephritis (LN).^{31,32} Schiffer *et al.* demonstrated that serum levels of CXCL13 in SLE patients were higher than those observed in healthy controls. In patients with LN, the level of this chemokine was even higher compared to those without LN.¹⁹

The influence of immunomodulation on the serum level of CXCL13 in SLE as in other immunomediated disorders is not yet known. In our

study the treatment regimen did not differ between the groups and although the proportion of patients taking glucocorticoids was higher in the JA group, there was no difference in the mean dose of prednisone between the groups.

In our study, there was no association between higher levels of CXCL13 and arthritis. These findings are different from those obtained by Bugatti *et al.*, who studied a cohort of RA patients and found that this chemokine could be the potential serologic marker for severity in RA as it was associated with synovial inflammation, which was confirmed by clinical examination and US.²³ On the other hand, we observed an association of the presence of tenosynovitis in US findings with higher levels of CXCL13, suggesting that it could be a potential biomarker for detecting tendon inflammation in SLE patients.

In the present study, US findings were more frequent in the JA group, especially synovitis and tenosynovitis, in all evaluated joints. These data support our previous study based on magnetic resonance imaging (MRI) in JA, suggesting that persistent synovial and tendon inflammation might be one of the potential mechanisms for the development of deformities in JA.³³ It could be a contributory factor for the previously described predisposition for tendon rupture in those patients.¹⁴

We also found erosions in two patients with JA (six joints). Similarly, Gabba *et al.* also demonstrated the presence of erosions by US in one of their six patients with JA.³⁴ By contrast, in our MRI study of JA, 16 out of 300 examined joints (5.3%) had small areas of erosion in 10 out of the 20 studied patients. These results could be due to the different joint sites investigated in our previous cohort (some of these not included in this study) and the natural low sensitivity of the US method for erosions. Also, the different erosive damage in JA did not resemble the condition seen in rhus syndrome or RA as recently described by Piga *et al.*³⁵

In conclusion, the present study is one of the first to describe US findings in joints of SLE patients with JA and confirms that synovitis and tenosynovitis are very common in these patients. In addition, serum level of CXCL13 is associated with disease activity in SLE but does not seem to be a biomarker for arthritis (clinically or by US) in SLE patients.

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Declaration of conflicting interests

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