Anti-cyclic citrullinated peptide antibodies in systemic lupus erythematosus patients with articular involvement: a predictive marker for erosive disease?

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SUMMARY

A small number of systemic lupus erythematosus (SLE) patients develops an erosive disease. Some studies have suggested an association between anti-cyclic citrullinated (anti-CCP) antibodies and this pattern of arthritis, but their exact significance in SLE patients remains unclear. The aim of this study was to evaluate the prevalence of anti-CCP antibodies in SLE patients with different subsets of articular disease.

Among 521 SLE patients followed in this center from 1976 to 2011, those with articular involvement (n=298) were selected to take part in the study. We searched for anti-CCP2 IgG antibodies in 198 patients using a commercial enzyme linked immunosorbent assay (Immunoscan RA, Eurodiagnostica). In 174 patients the results for rheumatoid factor (RF) by nephelometry were retrospectively collected. C reactive protein (CRP) was obtained from clinical records. Patients were classified into 3 groups: erosive, non-erosive deforming, non-erosive non-deforming arthritis. Results of the different tests were compared among the groups. $P<0.05$ was considered statistically significant. Anti-CCP antibodies were significantly associated with erosive disease. We also found that RF positivity and increased CRP were more frequent in erosive arthritis and erosive or non-deforming arthritis, respectively, than in non-erosive non-deforming arthritis.

This study supports the evidence that anti-CCP antibodies could be a useful marker of erosive disease in SLE patients. Increase in RF and CRP could be an additional means of identifying lupus patients with arthritis at risk of a worse prognosis.

Key words: *Systemic Lupus Erythematosus, anti-cyclic citrullinated peptide antibodies, arthtritis.*

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INTRODUCTION

Arthritis is one of the most common features of systemic lupus erythematosus (SLE), affecting 60-90% of patients during their clinical history (1). It can also be the presenting manifestation in a considerable proportion of patients and generally appears early during the disease course. Articular involvement in SLE is often a chronic problem with a significant impact on the disease and quality of life (2). Lupus arthropathy has variable expression with different severity, from transient arthritis to severe deforming arthritis (3).

The classical articular involvement in SLE patients is a non-erosive and non-deforming arthritis without significant functional consequences. A small number of SLE patients develops a deforming arthritis, due to the joint capsule and tendon laxity, known as Jaccoud's arthropathy (4) or an erosive disease, often called Rhupus for its clinical and prognostic similarity to rheumatoid arthritis (RA) (5). In these cases, and in particular in those patients who develop erosions, there can be a very strong impact of the disease on function and quality of life. Risk factors and the pathogenic mechanism of erosive arthritis are still not fully understood (6). Finding serological markers to distinguish the different articular subsets after early phases of the disease would be useful to establish a prognosis

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and select the correct clinical and therapeutic approach to the disease.

Anti-cyclic citrullinated (anti-CCP) antibodies are fully recognized as a diagnostic and prognostic marker with a high sensitivity and specificity for RA (7). Even if these antibodies were initially thought to be present only in RA patients, they have been found with a minor prevalence and at low levels in patients with other autoimmune diseases, including SLE (8). Over the past 15 years, some authors have suggested that anti-CCP antibodies are associated with erosive arthritis in SLE, but the exact significance of their presence in SLE remains unclear (9).

The aim of this study was to determine the prevalence of anti-CCP antibodies in SLE patients with different subsets of articular disease to evaluate their significance in this population. In particular, we were interested in clarifying whether anti-CCP are a useful tool to distinguish different subsets of SLE arthropathy.

MATERIALS AND METHODS

The clinical records of 521 SLE patients attending the Rheumatology Clinic at Spedali Civili of Brescia, Italy, from 1976 to 2011 were retrospectively reviewed. Patients with articular involvement (n=298, 57%), defined as arthritis in at least 2 joints at any time during the disease course, were selected to take part in the present study. They had all been diagnosed with SLE according to American College of Rheumatology (ACR) criteria (10).

X rays of hands, feet and other involved articular sites were obtained as decided by the clinician on an individual basis for each patient and these were reviewed to determine the presence of joint erosions.

Patients were classified into three groups:

a) *erosive* arthritis if erosions were found on X rays;
b) *non-erosive deforming* if classical reversible deformities were present (ulnar deviation, swan neck deformity, thumb subluxation) and no erosion was found on X rays (11);
c) *non-erosive non-deforming* in all other cases.

Sera collected during medical routine assessment and stored at -20°C were available for analysis in 198 patients, and these were included in this study. A commercial enzyme linked immunosorbent assay (Immunoscan RA, Eurodiagnostica) was used to evaluate the presence of anti-CCP2 IgG antibodies. A cut off of 25 UI/mL was used, as suggested by the manufacturer's protocol. In 174 patients, the results for rheumatoid factor (RF) by nephelometry and the serum level of C reactive protein (CRP) were obtained from clinical records.

Two-tailed Student's t-test for continuous variables and Fisher's exact test or Yates's χ^2 test for categorical variables were used. A multivariate analysis was conducted by a logistical regression model (Statview). $P<0.05$ was considered statistically significant. Odds Ratio (OR) and 95% Confidence Interval (CI95%) were calculated.

RESULTS

The demographic and serological data of the 198 patients included in the study are summarized in Table I. Most patients (n=190) were Caucasian, but there were 4 Africans and 4 Asians. The sample included 183 females and 15 males, with a mean age at arthritis onset of 32.29 years (standard deviation (SD) 13). Median follow up was of 11 years (range 1-28).

Among the 198 patients a non-erosive non-deforming arthritis was present in 157 (80%), a deforming arthritis in 32 (16%), and an erosive arthritis in 9 (4%). There were no statistically significant differences in sex or ethnic distribution or in mean age at arthritis onset among the 3 groups. Most patients had a hand involvement and polyarticular disease was the most frequent pattern, without significant differences between the 3 groups. All patients were positive for antinuclear antibodies detected by indirect immunofluorescence on Hep2 cells.

Anti-CCP antibodies were found in 15 patients (7%) and these appeared to be distributed differently among the differ-

Table I - Demographic and serological data of 198 SLE patients.

Patient characteristics	All patients (n=198, 100%)	Erosive arthritis (n=9, 4%)	Deforming arthritis (n=32, 16%)	Non-erosive non-deforming arthritis (n=157, 80%)
Caucasian, n. (%)	190 (95%)	9 (100%)	31 (97%)	150 (95%)
Female, n. (%)	183 (92%)	9 (100%)	30 (94%)	144 (92%)
Age at arthritis onset, mean (SD)	32.29 (13)	34.03 (15)	34.15 (12)	31.74 (14)
Hand involvement, n. (%)	155 (78%)	9 (100%)	29 (91%)	117 (75%)
Polyarticular involvement, n. (%)	147 (74%)	8 (89%)	28 (87%)	111 (71%)
Anti-CCP positivity, n. (%)	15 (7%)	4 (44%)*	3 (9%)	8 (5%)
Anti-CCP levels (mean±SD)	238.83±327	36.05±14	613.27±574	199.81±186
Increased CRP, n. (%)	74 (37%)	5 (55%)**	10 (31%)**	6 (4%)
RF positivity, n. (%)	34/174 (19%)	5/9 (55%)°	9/29 (31%)	20/136 (15%)
Anti-CCP and RF positivity, n. (%)	7/174 (4%)	2/9 (22%)°°	2/29 (7%)	3/136 (2%)
Anti-CCP and/or RF positivity, n. (%)	39/174 (22%)	6/9 (67%)§	10/29 (34%)	23/136 (17%)

SLE, systemic lupus erythematosus; n, number of patients; SD, standard deviation; anti-CCP, anti-cyclic citrullinated peptide antibodies; CRP, C reactive protein; RF, rheumatoid factor; *anti-CCP, erosive vs deforming arthritis: P=0.031; erosive vs non-erosive non-deforming arthritis: P=0.002; **increased CRP, erosive vs non-deforming arthritis: P<0.001, deforming vs non-erosive non-deforming arthritis: P<0.001; °RF positivity, erosive vs non-erosive non-deforming arthritis: P=0.008; °°anti-CCP and RF positivity, erosive vs non-erosive non-deforming arthritis: P=0.031; §anti-CCP and/or RF positivity, erosive vs non-erosive non-deforming arthritis: P=0.002.

ent subtypes of arthritis. In particular, patients with erosive arthritis were more frequently positive for anti-CCP antibodies than those with deforming (P=0.031, OR=7.7, CI95%=1.0-67.3) or non-erosive non-deforming arthritis (P=0.002, OR=14.9, CI: 95%=2.7-84.4). In any case, when anti-CCP levels in each group were compared no significant differences were observed. RF was observed in 34 patients (19%) among the 174 who were tested. Fifty-five percent of patients with erosive arthritis tested positive in contrast to 15% of patients with non-erosive non-deforming arthritis (P=0.008, OR=7.2, CI: 95%=1.5-35.9). Double positivity for anti-CCP antibodies and RF was mostly found in patients with erosive arthritis (22%) and was rare in patients with non-erosive non-deforming arthritis (2%) (P=0.031, OR=12.7, CI: 95%=1.2-121.5). A stronger association with erosive arthritis was found for the positivity for anti-CCP antibodies and/or RF (P=0.002, OR=9.83, CI: 95%=1.97-54.27). An increase in CRP was significantly more frequent in patients with erosive (P<0.001, OR=31.5, CI: 95%=5.4-199.7) or deforming arthritis (P<0.001, OR=11.4, CI: 95%=3.4-40.0) than in non-erosive non-deforming arthritis.

In a multivariate analysis, including anti-CCP antibodies, RF and CRP elevation, only anti-CCP were significantly associated to erosive arthritis (P=0.02, OR=6.87, CI: 95%=1.35-34.95). No association was found between the same serological parameters and deforming arthritis.

DISCUSSION

Like in RA, it would be very useful to have a serological marker capable of early identification of SLE patients at risk of erosive arthritis. In particular, such a marker could help to establish the most appropriate clinical and therapeutic approach for these patients in order to prevent irreversible articular damage.

Mediwake et al. (5) first suggested in 2001 that anti-CCP could be a useful marker to distinguish SLE patients with erosive disease, as these antibodies were prevalent (20%) in this type of arthritis and very rare in other forms (0-2%). This observation was initially supported by small case reports (6, 12, 13) and then confirmed in some larger samples of SLE patients with arthritis (9, 14-18). Two of these studies (6, 17) proposed that anti-CCP antibodies

could be a marker both of erosive and deforming arthritis in SLE patients, whereas another study (19) found no association between these antibodies and deforming arthritis. As anti-CCP antibodies can also be found in SLE patients without erosive arthritis or rarely without articular involvement (9, 18), Kakumanu et al. (17) investigated the citrulline dependence of these antibodies, finding that citrulline-dependent antibodies (reactive with citrullinated peptide but unreactive to the unmodified peptide containing arginine) are associated with erosive or deforming arthritis in SLE patients. This, together with high levels of anti-CCP, as previously suggested by Qing et al. (16), would be a potential specific marker for erosive disease. Anti-CCP prevalence among patients with various arthropathies in previous studies was extremely variable. This heterogeneity could be explained by the fact that patients with erosive arthritis were selected by different methods (in some cases ACR criteria for RA fulfilling, in other cases presence of erosions at X rays); this also makes it difficult to compare results.

Our study confirms the previously described association between anti-CCP antibodies and erosive arthritis. In contrast to the literature (16, 17), we found no association even with high levels of these antibodies, but this could be due to a smaller number of anti-CCP positive patients in our study compared to other studies.

Our findings also suggest that RF could be another useful marker to differentiate patients with erosive arthritis from non-erosive non-deforming arthritis. The three largest studies that analyzed this topic mostly found a significant association of RF with erosive (14, 15) and deforming (15) arthritis when prevalence was compared to that observed in patients with non-erosive non-deforming arthritis, even if this association was weaker than that of anti-CCP. In contrast, the study of Galvão et al. (19) found no differences in RF prevalence between patients with deforming arthritis and patients with non-deforming arthritis. We also found that double positivity for anti-CCP antibodies and RF was more prevalent in patients with erosive arthritis compared to those with non-erosive non-deforming arthritis, confirming that these two antibodies are able to identify a particular subset of patients, different from the classic benign articular SLE involvement. Even though a previous group suggested that a polyarticular hand involvement could be a predictive clinical marker of erosive disease (16), we found no predictive value for a specific SLE arthropathy pattern either of hand or of polyarticular involvement. Interestingly, as previously described (12), an increase in CRP could help to distinguish SLE patients with or without classic articular involvement. As CRP serum levels did not correlate with disease activity in SLE, in contrast to the majority of inflammatory diseases, this simple marker in SLE patients with articular involvement could be a warning signal of worse articular evolution.

In conclusion, our study supports the evidence that anti-CCP antibodies could be a useful marker of erosive disease in SLE patients. Increase in RF and CRP could be an additional instrument to identify patients at risk of the poorest prognosis. For these reasons, these three tests should be considered in the follow up of all SLE patients with articular disease.

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