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ORIGINAL ARTICLE

Are anti-CCP antibodies in psoriatic arthritis patients a biomarker of erosive disease?

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Abstract To determine the frequency of anticyclic citrullinated peptide (CCP) antibodies in a cohort of psoriatic arthritis (PsA) patients and to compare clinical, serological and radiological characteristics between PsA patients with and without anti-CCP antibodies. Patients with PsA, according to classification criteria for PsA, were consecutively recruited from an outpatient rheumatology clinic. Demographic and clinical data were collected in all cases. Serum samples from all patients were analyzed for rheumatoid factor and anti-CCP antibodies. Radiographs of hands and feet were obtained and the presence of erosions was recorded. The study included 81 patients; 43 (53 %) were men, with a median age of 45.7 years (interquartile range (IQR) 39–72) and median disease duration of 9.4 years (IQR 2–14). Anti-CCP antibodies were found in 11 patients (13.5 %), median titer 174.9 U/ml. Polyarticular involvement (72.7 vs. 17.1 %), frequency of erosive disease (72.7 vs. 37.1 %) and use of tumor necrosis factor-α inhibitors (54.5 vs. 28.5 %) were significantly higher in PsA patients with anti-CCP positivity. Anti-CCP negative PsA patients had predominantly more oligoarticular (62.8 vs. 27.2 %) and nail (81.4 vs. 36.3 %) involvement. Presence of enthesitis, dactylitis and Psoriasis Area Severity Index scores were similar in both groups. Anti-CCP antibodies were found in a subset of PsA patients, and their presence was associated with more severe disease phenotype. Further studies in a larger population are needed to define the role of anti-CCP as a biomarker of erosive disease in PsA.

Keywords Anti-CCP antibodies · Psoriatic arthritis · Disease severity · Radiographic damage

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Introduction

Psoriatic arthritis (PsA) is a clinically heterogeneous disorder with diverse phenotypes of peripheral and axial joint involvement, and also extra-articular manifestations including skin, nails, entheses and dactylitis. Moll and Wright [1] recognized PsA as a distinct clinical entity, but ever since there has been considerable debate whether or not PsA constitutes a distinct entity, separate from rheumatoid arthritis (RA). A school of thought considers PsA as the coincident occurrence of a seronegative arthropathy and cutaneous psoriasis. Peripheral joint involvement in early PsA has been described to be fundamentally oligoarticular; however, in some circumstances, patients may present with polyarthritis, being difficult to distinguish from RA. Indeed, in PsA patients, progression from asymmetric oligoarticular to symmetric polyarticular disease over time appears to be the norm [2, 3].

On the other hand, antibodies recognizing cyclic citrullinated peptides (CCP) are characteristic and specific markers of RA, and their presence especially at high titers is associated with a more aggressive and erosive disease [4, 5]. However, despite the reports of the high specificity of anti-CCP antibodies seen in RA, different authors have reported the presence of anti-CCP in other chronic

rheumatic disorders, including PsA, Sjögren's syndrome [6], scleroderma [7], Behcet's disease [8] and systemic lupus erythematosus [9–12].

The prevalence, clinical significance and potential pathogenicity of anti-CCP positivity in PsA patients have been the topic of recent discussion. Presence of anti-CCP in PsA is reported to be around 10 %, but ranges as low as <1 % and as high as 16 % in some published series [13–18]. In general, it has been suggested that the presence of anti-CCP antibodies in PsA is concordant with a symmetric polyarticular joint involvement, a more aggressive and erosive disease course and that its presence should be followed by more aggressive treatment modality, just as in RA [19, 20].

Therefore, based on these observations, the aim of this cross-sectional study was to assess the frequency and clinical significance of anti-CCP positivity in a cohort of PsA patients.

Materials and methods

Patient selection

Patients with PsA were recruited consecutively from an outpatient rheumatology clinic, during a period of 1 year. All patients fulfilled classification criteria for psoriatic arthritis (CASPAR) [21]. Presence of a positive rheumatoid factor (RF) did not exclude the patient from the study, if typical clinical and radiological features [e.g., new bone formation, pencil-in-cup, joint ankylosis, predominance of distal interphalangeal (DIP) involvement and sacroiliitis] suggestive of PsA were present.

Clinical evaluation

All patients underwent a complete evaluation, including demographic (age and gender) and clinical data (family history of psoriasis and PsA, disease duration, peripheral and axial disease, nail involvement, dactylitis and enthesitis). PsA patients were divided into five groups: exclusive DIP involvement, oligoarthritis (with fewer than five involved joints), polyarthritis (≥5 involved joints), axial predominant involvement and arthritis mutilans (with severe, destructive and marked joint deformity of hand or foot) [22]. Information on joint peripheral involvement was recorded, and 68 tender and 66 swollen joint counts were assessed in each patient. Entheseal involvement was assessed in the following anatomic regions: bilateral first and seventh costochondral joints, lateral epicondyles of the elbows, medial femoral condyles, fifth lumbar spinous process, anterior superior iliac spines, iliac crests, posterior superior iliac spines, Achilles tendons and plantar fascia. Clinical enthesitis was defined as a tender enthesis. Dactylitis was defined as a uniform swelling of soft tissues between the metacarpophalangeal joint and digital tuft. Axial involvement was defined by the presence of chronic inflammatory back pain (>3 months) with radiographic evidence of sacroiliitis [23]. A dermatologist using Psoriasis Area Severity Index (PASI) score evaluated psoriasis involvement. Treatment data, regarding use of disease-modifying antirheumatic drugs (DMARDs) and tumor necrosis factor alpha (TNF-α) blockers, were also recorded.

Plain radiographs of hands, wrists and feet were performed in all patients at initial presentation. At least one definitive erosive change was considered sufficient for inclusion of the patient to the erosive group. Subjects were classified as having either erosive or non-erosive disease.

Laboratory analysis

All collected sera were stored at <20 °C before testing. Anti-CCP antibodies were measured in all patients using a commercially available second-generation enzyme-linked immunosorbent assay (ELISA), from INOVA Diagnostic, Inc. (San Diego, CA, USA) following the manufacturer's instructions, establishing a cutoff point of >20 U/ml for a positive test. IgM-RF was examined in the sera by nephelometry, and titers higher than 14 U/ml were considered positive.

The local ethical committee approved the study and written informed consent according to the Declaration of Helsinki was obtained from all patients.

Statistical analysis

Comparisons for categorical variables were made by Fisher's exact test and χ^2 when appropriate. Continuous variables were compared by Student's t test. Comparisons between the two groups of patients (CCP positive and CCP negative) were carried out using Kruskal–Wallis nonparametric analysis of variance. A value of $p < 0.05$ was considered significant. The SPSS for Windows software, version 12.0 (SPSS, Chicago, IL, USA) was used for the analysis.

Results

The study included 81 patients with PsA; demographic and clinical characteristics of the cohort are summarized in Table 1. Briefly, 43 patients (53 %) were men; the median age was 45.7 years (IQR 39–72), with a median of disease duration of 9.4 years (IQR 2–14). Most patients had oligoarticular involvement (58 %), followed by polyarthritis in 25 % of patients. The median PASI score was 7.1 (IQR 6–9.4). Regarding treatment, 77 patients (95 %) were receiving DMARDs and 26 (32 %) were on anti-TNF-inhibitors in addition to DMARDs.

Table 1 Psoriatic arthritis: clinical and demographic features ($n = 81$)

Variables	$n = 81$
Demographic features	
Male [*n* (%)]	43 (53)
Median age [*m* IQR (years)]	45.7 (39–72)
Median disease duration [*m* IQR (years)]	9.4 (2–14)
Family history of psoriasis [*n* (%)]	13 (16)
Clinical features	
Oligoarthritis [*n* (%)]	47 (58)
Polyarthritis [*n* (%)]	20 (24.6)
DIP involvement [*n* (%)]	13 (16)
Enthesitis [*n* (%)]	6 (7.4)
Dactylitis [*n* (%)	5 (6.1)
Nail involvement [*n* (%)]	61 (75.3)
Axial involvement [*n* (%)]	6 (7.4)
Arthritis mutilans [*n* (%)]	3 (3.7)
Median PASI score (*m* IQR)	7.1 (6–9.4)
Laboratory features	
Anti-CCP positive [*n* (%)]	11 (13.5)
Anti-CCP [*m* IQR (U/ml)]	174.9 (26.2–453)
RF positive [*n* (%)]	9 (11.1)
Treatment	
DMARDs [*n* (%)]	77 (95)
TNF-α inhibitors [*n* (%)]	26 (32)

DIP distal interphalangeal joint, *PASI* Psoriasis Area Severity Index, *Anti-CCP* anticyclic citrullinated peptides, *RF* rheumatoid factor, *DMARDs* disease-modifying antirheumatic drugs, *TNF-α* tumor necrosis factor alpha, *IQR* interquartile range

Anti-CCP positivity was found in 11 patients of our PsA cohort (13.5 %). Titers of anti-CCP antibodies found ranged from 26.2 to 453 U/ml, with a median titer of 174.9 U/ml. Five of them were also positive for RF.

The clinical features of anti-CCP positive patients are detailed in Table 2. Most patients were female (81.8 %) and had polyarticular involvement (72.7 %) and erosive disease (72.7 %).

Clinical features between PsA patients with and without anti-CCP positivity

As shown in Table 3, we found some differential features among PsA patients with and without anti-CCP positivity. Median age and disease duration were similar in both groups. However, in contrast to the anti-CCP negative PsA cohort, most PsA patients with positive anti-CCP antibodies were females ($p < 0.05$) and specially exhibited significantly more symmetric polyarthritis (72.7 vs. 17.1 %, $p < 0.05$), higher frequency of erosive disease (72.7 vs. 37.1 %, $p < 0.05$) and less nail involvement (36.3 vs. 81.4 %, $p < 0.05$). Anti-CCP negative PsA patients had predominantly more oligoarticular involvement (62.8 vs. 27.2 %, $p < 0.05$). No significant differences regarding enthesitis, dactylitis, axial involvement and PASI scores were found in both groups ($p =$ NS). The frequency of RF positivity was also higher in anti-CCP positive PsA patients (45 vs. 5.7 %, $p < 0.05$). Regarding treatment, significantly more anti-CCP positive patients were on anti-TNF-α therapy (54.5 vs. 28.5 %, $p < 0.05$). No significant differences were found regarding frequency of DMARDs therapy.

Discussion

Anti-CCP antibodies may be present, albeit in low frequency (1–16 %) in PsA patients, especially in those with polyarticular involvement, high disease activity and more radiological damage [13–20]. It is quite possible that the

Table 2 Characteristics of PsA patients with positive anti-CCP antibodies ($n = 11$)

Patient no	Gender	Disease durat [m (years)]	Pattern of joint involvement	PsA clinical features	Erosive disease	Anti-CCP [*m* (U/ml)]	RF status
1	F	12	Polyarticular	DIP involvement	Yes	142.9	(−)
2	F	14	Polyarticular	Nail involvement	Yes	123.3	(−)
3	F	4	Polyarticular	DIP involvement	Yes	157.6	(+)
4	F	12	Polyarticular	Enthesitis–dactylitis	No	180.2	(−)
5	F	8	Polyarticular	Dactylitis	No	133.6	(−)
6	F	6	Oligoarticular	DIP involvement	Yes	49.7	(−)
7	M	5	Oligoarticular	DIP involvement	Yes	26.2	(−)
8	F	2	Polyarticular	Nail and DIP involvement	Yes	435	(+)
9	F	2	Polyarticular	Enthesitis	Yes	>250	(+)
10	F	12	Polyarticular	Nail involvement enthesitis	Yes	>250	(+)
11	M	7	Oligoarticular	Nail–axial–DIP involvement	No	>250	(+)

PsA psoriatic arthritis, *DIP* distal interphalangeal joint, *Anti-CCP* anticyclic citrullinated peptides, *RF* rheumatoid factor

Table 3 Psoriatic arthritis: differences between patients with and without anti-CCP antibody positivity

Variables	Anti-CCP (+) patients ($n = 11$)	Anti-CCP (−) patients ($n = 70$)	p value
Demographic features			
Median age [*m* IQR (years)]	53.2 (42–74)	47.7 (39–72)	NS
Female gender [*n* (%]	9 (81.8)	38 (54.2)	<0.05
Disease duration [*m* IQR (years)]	8.9 (3–15)	9 (6–14)	NS
Clinical features			
Polyarthritis [*n* (%)]	8 (72.7)	12 (17.1)	<0.05
Oligoarthritis [*n* (%)]	3 (27.2)	44 (62.8)	<0.05
Monoarticular (DIP) [*n* (%)]	6 (54.5)	8 (11.4)	<0.05
Axial involvement [*n* (%)]	1 (9)	5 (7.1)	NS
Enthesitis [*n* (%)]	3 (27.2)	3 (4.2)	NS
Dactylitis [*n* (%)]	2 (18.1)	3 (4.2)	NS
Nail involvement [*n* (%)]	4 (36.3)	57 (81.4)	<0.05
PASI score (*m* IQR)	10 (8.2–11.5)	7.1 (6–9.4)	NS
Erosive disease [*n* (%)]	8 (72.7)	26 (37.1)	<0.05
RF positive [*n* (%)]	5 (45.4)	4 (5.7)	<0.05
Treatment			
DMARDs [*n* (%)]	9 (81.8)	68 (97.1)	NS
TNF-α inhibitors [*n* (%)]	6 (54.5)	20 (28.5)	<0.05

Anti-CCP anticyclic citrullinated peptides, *DIP* distal interphalangeal joint, *PASI* Psoriasis Area Severity Index, *RF* rheumatoid factor, *DMARDs* disease-modifying antirheumatic drugs, *TNF-α* tumor necrosis factor alpha, *IQR* interquartile range

variability observed in prevalence rates among different studies may be related to the PsA classification criteria used, as most studies with low anti-CCP antibody positivity rates (below 5 %) use the Moll and Wright criteria, which selectively excludes PsA patients with RF positivity. In our study, anti-CCP antibody positivity was present in five patients with RF positivity. It should be noted that RF positivity may be found in low frequency in several chronic inflammatory disorders including psoriasis and PsA, and according to current classification criteria, there is no reason to exclude a PsA diagnosis if typical clinical and radiological features are present [21–25].

The clinical distinction between RA and PsA is often difficult to establish, particularly in polyarticular PsA forms. Anti-CCP antibody positivity may be a useful marker in establishing the correct diagnosis in most patients, since these antibodies are highly sensitive and specific in RA and have been shown to be associated with a more severe disease and radiological progression. The presence of anti-CCP antibodies in a small subset of PsA patients, primarily with polyarticular involvement, as well as in other connective tissue disorders, also appears to be a marker of a more severe disease with erosive articular involvement [12]. Our findings are in agreement with these observations considering that we found a subset of PsA patients (13.5 %) with anti-CCP antibody positivity, with a median titer of 174.9 U/ml, and as a group tended to have a preponderance of females, a more aggressive polyarticular and erosive disease involvement, and higher use of anti-TNF-α therapy. When compared with our PsA patients, significantly higher mean levels of CCP antibodies have been found only in cohorts of RA patients. Inanc et al. [16] reported a mean anti-CCP titer of 446 ± 479 U/ml in a cohort of RA patients. Yang et al. [26] found higher levels of CCP antibodies among RA patients, especially in smokers (242.7 ± 128.3 U/ml). Previously, Caspi et al. [27] have shown significantly higher levels of anti-CCP antibodies in RA patients (115 ± 120 U/ml) in comparison with PsA patients (62 ± 94 U/ml).

There is some suggestion that the presence of anti-CCP antibodies in PsA may predict disease progression, especially in patients with oligoarticular involvement. Alenius et al. [17] described an anti-CCP prevalence of 7 % in PsA, with 8 of 11 patients exhibiting polyarticular involvement, and fulfilling ACR criteria for RA at 4-year follow-up. Interestingly, five of these eight PsA patients initially presented with DIP involvement. Korendowych et al. [13] also showed an increased prevalence of anti-CCP antibodies in their PsA population associated with disease severity and with the presence of HLA-DRB1 shared epitope.

The expression of CCP in synovial fluid (SF) and tissue is not specific for RA and can be demonstrated in spondyloarthritis including PsA, but the local induction of autoantibodies directed to these peptides is a specific feature only in RA patients [28, 29]. However, Spadaro et al. have reported that anti-CCP antibodies are present in PsA-SF,

albeit in lower concentration as compared to RA, and that their presence or absence did not discriminate a particular PsA subset [30].

It remains to be determined whether the coexistence of PsA and anti-CCP antibodies identifies a specific subset of PsA, an overlap syndrome (PsA with RA) or the co-occurrence of psoriasis with concomitant RA. In our cohort, all but one of patients with RF positivity had also high levels of anti-CCP (>250 U)/ml. However, an analysis of the characteristics observed in our PsA patients leads us to conclude that PsA is the more likely diagnosis in our anti-CCP positive group. All of them exhibited at least one of the typical findings of PsA, such as dactylitis, enthesitis, axial, DIP involvement, nail and cutaneous psoriasis, as well as radiological features (new bone formation, pencil-in-cup deformity, joint ankylosis, DIP involvement and sacroiliitis). Vander Cruyssen et al. [15] reached a similar conclusion after a detailed analysis of their PsA cohort.

Our group of PsA patients with anti-CCP positivity revealed higher frequency of erosive disease and also more exposure to anti-TNF-therapy. Although it seems contradictory, we assume this discrepancy as a reflection of a more severe disease, even refractory to first-line therapy (DMARDs).

Our report has some limitations, mostly inherent to the cross-sectional and mostly descriptive nature of the study. Another issue that could affect the results of this study is related to the small sample size of our PsA cohort, including the few patients with anti-CCP positivity, that might limit the statistical power for several analysis of its association with different clinical features of the disease. In addition, we could not assess the progression of the disease, or the potential prospective effect of the use of DMARDs and biologic therapy on radiographic damage. As all patients were recruited from a tertiary referral center, our study might have omitted patients with mild disease activity and/or good prognosis. Also, we could not adjust our analysis for other possible confounders, such as socioeconomic status, as no data were available on this topic. Furthermore, we did not perform genetic analysis in order to assess the relationship between shared epitope, anti-CCP antibodies and radiological damage.

In conclusion, our findings clearly confirm previous reports demonstrating that the presence of anti-CCP antibodies occurs in a subset of PsA patients. In our PsA cohort, anti-CCP positivity identified a subgroup with significantly higher frequency of symmetric polyarticular involvement, severe disease activity, erosive disease and higher use of biologic therapy. It remains to be determined, however, whether anti-CCP antibodies do have a pathogenic role in PsA. Overall, the findings lend to support the notion that anti-CCP antibody, when present, should be considered a marker of disease severity in patients with PsA. Further studies, however, in larger number of patients are needed to truly establish the role of these antibodies in PsA.

Conflict of interest The authors declare that they have no conflict of interest.

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