Antibodies to Cyclic Citrullinated Peptides in Psoriatic Arthritis

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ABSTRACT. ***Objective.*** To determine the presence and clinical significance of antibodies to cyclic citrullinated peptides (anti-CCP) in psoriatic arthritis (PsA).

Methods. We performed a cross-sectional study on 102 outpatients (56 men) with PsA consecutively recruited from a tertiary referral center. Median disease duration was 36 months (interquartile range 21-81). All patients were investigated for peripheral joint and axial involvement, enthesitis, and dactylitis. Laboratory investigations included anti-CCP, assessed by enzyme-linked immunosorbent assay and IgM rheumatoid factor (RF). Plain radiographs of pelvis, wrists, hands, and feet were performed in all cases.

Results. Anti-CCP were detected in 16/102 patients, 8/68 with symmetric polyarthritis, 1/8 with asymmetric polyarthritis, 2/20 with mono-oligoarthritis, 1/2 with mutilating arthritis, and 0/4 with exclusive axial or distal interphalangeal (DIP) involvement. The male:female ratio as well as frequency of dactylitis, enthesitis, and nonexclusive axial or DIP joint involvement were similar in the anti-CCP positive and negative groups. Anti-CCP positive patients were more frequently treated with disease modifying antirheumatic drugs and showed higher number of involved joints, and higher frequency of erosive arthritis and positive RF. Using multiple logistic regression, anti-CCP (but not RF) were significantly associated with erosive arthritis (odds ratio 9.8; 95% confidence interval 1.87-51.8) and ≥ 10 involved joints (17.99; 3.6-89.2).

Conclusion. Anti-CCP can be found in a small but significant proportion of patients with a clinical picture of PsA and are associated with erosive arthritis and multiple joint involvement. (J Rheumatol 2005;32:511–5)

Key Indexing Terms:
PSORIATIC ARTHRITIS RHEUMATOID ARTHRITIS EROSIONS
ANTI-CITRULLINATED PEPTIDE ANTIBODIES RHEUMATOID FACTOR

Psoriatic arthritis (PsA) was recognized as a distinct clinical entity more than 40 years ago[1,2] and in 1973 Moll and Wright[3] identified 5 different clinical subsets. In the following years, the concept of PsA and its relationship with either rheumatoid arthritis (RA) or seronegative spondyloarthropathies have continuously evolved[4], leading to proposals for modification of the Moll and Wright classification criteria or new clinical subsets[5-13].

The relative frequency of the different clinical subsets is greatly variable from study to study. In earlier studies peripheral oligoarthritis was reported as the most frequent clinical pattern. In contrast, several recent studies indicated a prevalence of peripheral polyarthritis ranging from 37% to 70%[13-15]. Furthermore, while asymmetric joint involvement had been regarded as characteristic of PsA, some recent surveys have reported symmetrical polyarthritis in more than 60% of cases[15]. It is now evident that many patients in PsA will change their initial clinical pattern from oligoarthritis to polyarthritis, and from asymmetrical to symmetrical joint involvement during the disease course[16].

Taking into account these findings, the differential diagnosis between PsA and RA in a patient with psoriasis may be difficult[17]. The Moll and Wright criteria excluded RF positive patients from a diagnosis of PsA. However RF was found in as many as 13% of patients with psoriasis and in PsA as well[15]. Furthermore, RF can be found in other unrelated chronic disorders, including hepatitis C virus (HCV) related conditions[18] and in elderly people[19]. Thus, some recently proposed criteria for PsA allow the possibility of classifying a patient with PsA despite a positive test for RF[8,9]. The presence of rheumatoid nodules could lead to a diagnosis of RA; however this seems of little help in Mediterranean countries where subcutaneous nodules are found in about 10% of RA patients and occur late in the course of the disease[20].

Antibodies directed against epithelial intermediate filament-associated protein filaggrin[21] including anti-keratin

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Submitted June 7, 2004; revision accepted October 22, 2004.

antibodies and anti-perinuclear factors, were reported to be quite specific for RA, although several positive cases have been reported in PsA[22,23].

Recently it has been shown that filaggrin citrullination is an essential step for immunogenicity[24], and cyclic citrullinated peptides (CCP) are currently used as antigens in enzyme-linked immunosorbent assays (ELISA). Since the development of ELISA for antibodies to CCP, these antibodies have shown a strong specificity for the diagnosis of RA[25-27]. In addition, anti-CCP have been detected with a significantly higher prevalence in sera of RA patients who will develop severe radiological damage[28,29]. The role of anti-CCP in identifying patients at risk of more severe disease might be of great importance since early and aggressive therapy might prevent the progression of joint damage.

To date, no study has specifically addressed anti-CCP in PsA. Our work deals with a cross-sectional analysis of 102 outpatients with PsA to evaluate the frequency of occurrence and clinical associations of anti-CCP antibodies in this clinical setting.

MATERIALS AND METHODS

Patients. One hundred and two Caucasian patients consecutively observed for PsA from March 2002 to December 2002 at the Rheumatology Department of the University Hospital of Pavia (Italy) were studied. All patients had both arthritis, assessed by an experienced rheumatologist, and psoriasis confirmed by a dermatologist. The patients with isolated enthesitis[30] or with PsA *sine psoriasis*[31] were not included. A positive test for RF was not considered an exclusion criterion. All patients underwent a careful evaluation including clinical history, physical examination, and routine radiographic and laboratory investigations. After informed consent according to the local Ethical Committee recommendations, an additional serum sample was collected and stored at -70˚C for anti-CCP determination. Demographics and main clinical characteristics of study patients are reported in Table 1.

Clinical evaluation. According to the Moll and Wright criteria, modified by Helliwell, *et al*[13], the following subgroups were identified: exclusive distal interphalangeal (DIP) involvement; exclusive axial involvement; mono- or oligoarthritis, i.e., < 5 involved joints; polyarthritis, i.e., ≥ 5 involved joints (considered symmetrical when bilateral involvement > 50% of affected joint areas was present[32]); and mutilating arthritis, i.e., severe, destructive arthritis of hand or foot interphalangeal joints, with at least one telescopic finger.

Information on joint involvement was obtained by physical examination of 68 joints for tenderness, deformity, and limited range of motion, and by physical examination of 66 joints for swelling[33]. Every patient was also evaluated for the presence or a positive history of dactylitis. Enthesitis and axial involvement along with peripheral arthritis were also assessed. Enthesitis was defined as present or past spontaneous pain or tenderness at examination of the site of insertion of the Achilles tendon, plantar fascia, and lateral or medial epicondyle. Axial involvement was defined by either inflammatory spinal pain, alternating buttock pain, or radiographic evidence of bilateral sacroiliitis grade 2 to 4 or unilateral sacroiliitis grade 3 to 4 according to the European Spondyloarthropathy Study Group specifications[11].

In addition, plain radiographs of hands, wrists, and feet were performed in all patients to evaluate the presence of erosions at the classical RA sites according to the Sharp-van der Heijde score[34].

Routine laboratory investigations included Westergren erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), and RF measured by immunonephelometry using the quantitative N Latex RF system (Dade Behring, Marburg, Germany). RF concentrations higher than 15 IU/ml were considered positive, as recommended by the manufacturer.

Table 1. Main demographic and clinical findings in 102 patients with PsA.

Variable	n
N	102
Median age, yrs	*56 (49–66)
Median disease duration, months	*36 (21–84)
Male/female	56/46
Palmoplantar pustulosis	3
Subcutaneous nodules	1
Axial involvement (all patients)	39
Exclusive axial involvement	3
DIP involvement (all patients)	46
Exclusive DIP involvement	1
Enthesitis	49
Dactylitis	38
Mono- or oligoarthritis	20
Asymmetric polyarthritis	8
Symmetric polyarthritis	68
Mutilating arthritis	2
Involved joints	*10 (6–12)
Swollen joints	*2 (0–4)
Erosive arthritis	38
DMARD therapy	65
Association therapy (≥ 2 DMARD)	23
ESR	*21 (10–45.7)
Serum CRP, mg/dl	*1.2 (0.5–2.66)
RF positive	19
Anti-CCP positive	16

* median (interquartile range).

Anti-CCP antibodies. Anti-CCP were tested using commercially available, second generation ELISA kits (Axis-Shield, Dundee, UK) on sera from 102 patients with PsA and 30 normal blood donors matched for age and sex.

Briefly, 100 µl of anti-CCP standards (0, 2, 8, 30, and 100 U/ml), control and patient samples (diluted 1:100 in phosphate buffer) were dispensed into the appropriate wells coated with a highly purified synthetic cyclic peptide containing modified arginine residues. After incubation for 60 min, the wells were washed 3 times with 200 µl of borate buffer containing 0.8% sodium azide. The microplates were then incubated for 30 min at room temperature with alkaline phosphate-labeled murine monoclonal antibody to human IgG and washed again 3 times. A chromogenic substrate solution (Mg_2 phenolphthalein monophosphate buffer solution) was added to each well. After 30 min the reaction was stopped using sodium hydroxide-EDTA-carbonate buffer. The absorbance was read at 550 nm. Serum samples were evaluated in triplicate and the upper normal limit (5 UI/ml) was assumed according to the manufacturer's recommendations. All control samples showed values < 5 UI/ml.

Statistical analysis. Association between anti-CCP and nominal variables was evaluated by Fisher's exact test. Association between anti-CCP and continuous variables was evaluated by the Mann-Whitney test. The association of anti-CCP or RF with the presence of erosions and the number of involved joints was analyzed using multiple logistic regression. All statistical analyses were performed using a StatView system.

RESULTS

Anti-CCP frequency and associated features. Among the 102 patients with PsA in this study, 16 were positive for anti-CCP. All anti-CCP positive cases showed high serum

levels with respect to the cut-off value, with a median value > 100 U/ml (range: 47 to > 100).

The 3 patients with exclusive axial involvement and the only patient with exclusive DIP involvement were anti-CCP negative, while at least one positive test was found in each of the other clinical subgroups. The frequency of anti-CCP in symmetrical polyarticular disease (12/68) was similar to that found in mono-oligoarthritis and asymmetric polyarthritis (3/28).

The comparison between anti-CCP positive patients and the other patients regarding the main demographic, clinical, radiographic, and laboratory features is reported in Table 2. No significant differences were in the presence of axial involvement, DIP involvement, enthesitis, or dactylitis. In contrast, the number of patients with erosive arthritis, radiologic score, and the proportion of patients treated with disease modifying antirheumatic drugs (DMARD), either alone or in combination, was significantly higher in the anti-CCP positive group. Furthermore anti-CCP positive patients had an increased number of involved and swollen joints.

The frequency distribution of joint involvement in patients with polyarthritis grouped according to their anti-CCP status is shown in Figure 1.

Anti-CCP and RF. A positive RF was found in 19 patients, and anti-CCP were present in 11 of them. The frequency of RF and anti-CCP in different clinical subgroups is reported in Table 3. As for the main clinical variables, a positive RF test was associated only with the use of DMARD, which was recorded in 15 out of 19 (79%) RF-positive patients and in 50 out of 83 (60%) RF-negative patients (p = 0.035). No significant correlation was found with any other variables investigated.

In particular, using multiple logistic regression analysis where anti-CCP and RF were independent variables, we found that only anti-CCP was associated with an increased risk of both erosive disease and ≥ 10 involved joints (Table 4).

Table 2. Main demographic and clinical variables in the anti-CCP positive group compared with the remaining (anti-CCP negative) patients with PsA.

	Anti-CCP + n (%)	Anti-CCP – n (%)	p
Age, yrs	*52 (42–62)	*58 (49.5–67)	0.269
Male/female	10/6	46/40	0.597
Disease duration, months	*48 (21–81)	*36 (21–84)	0.902
Palmoplantar pustolosis	0	3 (3.49)	> 0.999
Axial involvement (all)	6 (37.5)	33 (38.37)	> 0.999
Axial exclusive	0	3 (3.49)	> 0.999
DIP involvement (all)	7 (43.75)	39 (45.35)	> 0.999
DIP exclusive	0	1 (1.16)	> 0.999
Mono-oligoarthritis	2 (12.5)	18 (20.93)	0.732
Asymmetrical polyarthritis	1 (6.25)	7 (8.14)	> 0.999
Symmetrical polyarthritis	12 (75)	56 (65.11)	0.568
Mutilating arthritis	1 (6.25)	1 (1.16)	0.290
Dactylitis	5 (31.25)	33 (38.37)	0.417
Enthesitis	7 (43.75)	42 (48.84)	0.787
Involved joints	*15 (10.5–24)	*6 (5–10)	< 0.0001
Swollen joints	*2.5 (2–6.5)	*1 (0–2)	0.0033
Bone erosions	11 (68.65)	27 (31.39)	0.009
Sharp-van der Heijde score	*26 (0–59)	*0 (0–17)	0.019
ESR	*28.5 (15–56.15)	*20 (10–45)	0.365
CRP	*1.15 (0.7–3.45)	*1.21 (0.5–2.54)	0.665
RF+	11 (68.65)	8 (9.30)	0.0001
DMARD therapy	15 (93.75)	50 (58.14)	0.013
Association therapy, ≥ 2 DMARD	8 (50)	15 (17.44)	0.008

* median (interquartile range).

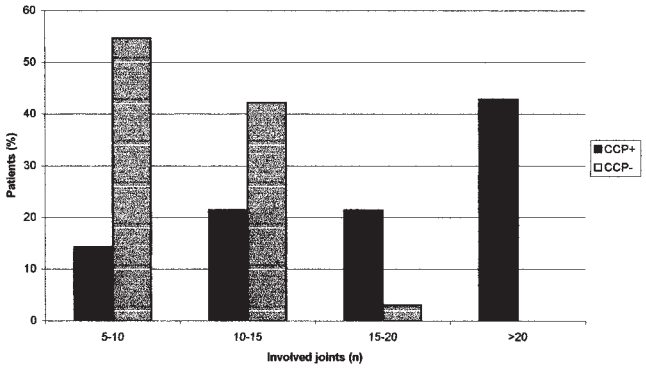

Figure 1. Number of involved joints in patients with psoriatic arthritis and polyarticular disease (≥ 5 affected joints) according to the presence of anti-CCP antibodies. Black bars: anti-CCP positive patients; gray bars: anti-CCP negative patients.

DISCUSSION

Anti-CCP antibodies were found in 16 of 102 patients (15.7%). Although our series is probably not representative of the whole spectrum of PsA, our results suggest that a serologic profile typical of RA can be observed in a small but significant proportion of PsA. This may represent a diagnostic challenge in patients with polyarticular disease.

A symmetric polyarticular pattern was encountered in 68% of our patients. This figure may be higher than that found in population based studies since the purely enthesitic forms were excluded from our study. Also, it is possible that a number of patients with mild disease and limited joint involvement might not have been referred to our center. However a prevalent symmetrical polyarticular involvement has been reported in several studies on PsA patients recruited from tertiary referral centers[15,16,32].

The occurrence of anti-CCP was not limited to the symmetric polyarthritis subgroup, since more than 10% of patients with either mono-oligoarthritis or asymmetric polyarthritis were positive for anti-CCP and RF. Since peripheral joint involvement in PsA tends to increase and become symmetric over time[16], it is possible that these patients will develop symmetric polyarthritis during the course of the disease.

One finding of interest is the similar prevalence of enthesitis, dactylitis, and axial or DIP involvement in the anti-CCP positive patients compared to the anti-CCP negative

Table 3. Frequency of anti-CCP antibodies and RF in the different clinical subsets of PsA.

Subset of PsA	Patients n	RF + n (%)	CCP + n (%)	RF + and CCP + n (%)
Axial exclusive	3	0	0	0
DIP exclusive	1	0	0	0
Mono/oligoarthritis	20	6 (30.0)	2 (10.0)	2 (10)
Polyarthritis (symmetric)	68	11 (16.2)	12 (17.6)	7 (10.3)
Polyarthritis (asymmetric)	8	1 (12.5)	1 (12.5)	1 (12.5)
Mutilating arthritis	2	1 (50.0)	1 (50.0)	1 (12.5)
Total	102	19 (18.6)	16 (15.7)	11 (10.7)

DIP: distal interphalangeal.

Table 4. Statistical probability level for risk of > 10 involved joints and the presence of erosion in patients positive for anti-CCP and RF.

	Anti-CCP Positive		RF Positive	
	OR (95% CI)	p	OR (95% CI)	p
Erosions	9.8 (1.87–51.8)	0.007	0.34 (0.07–1.7)	0.18
≥ 10 involved joints	17.99 (3.6–89.2)	0.0004	0.89 (0.2–3.9)	0.87

OR: odds ratio; CI: confidence interval.

group. The male:female ratio was also similar in both groups. This means that anti-CCP are not restricted to those patients with a clear-cut clinical picture of RA, as they may be present in patients with features usually regarded as typical of PsA and seronegative spondyloarthropathies. It seems likely from these data that a proportion of patients with true PsA may develop anti-CCP even though we cannot exclude the possibility that if RA should occur by chance in a patient with psoriasis it may show PsA-like clinical features. One of the anti-CCP positive patients in our series had symmetric erosive polyarthritis, with RF and histologically proven rheumatoid nodules, along with mutilating arthritis, grade 3 unilateral sacroiliitis, and recurrent episodes of dactylitis. Thus it seems difficult to establish whether this patient had PsA-like RA, RA-like PsA, or both.

Of interest, only 6 out of 16 patients anti-CCP positive had unmistakable evidence of PsA, while the remaining patients could have had RA coexisting with psoriasis. From a pragmatic point of view, therefore, our findings do not change the reported specificity of anti-CCP testing in RA.

It seems important to note that anti-CCP are associated with a higher number of involved and swollen joints in patients with polyarthritis, as well as with erosive arthritis and clinically aggressive disease needing DMARD therapy. The proportion of anti-CCP positive patients in PsA is much lower than reported in RA. However in PsA, as in RA[29,35], anti-CCP antibodies may be useful in detecting those patients with an increased risk of erosions and possibly requiring early DMARD treatment with conventional drugs or biological agents[36]. Prospective studies are warranted in this clinical setting.

In our patients, the association of anti-CCP with erosive arthritis was stronger than that of RF and independent of RF. Similar data have been reported in RA patients[29]. In some patients, RF may be unrelated to arthritis. For instance, HCV infection occurs in 5 to 10% of adult people in Northern Italy and is often asymptomatic[37]; this may lead to an increased rate of RF in otherwise seronegative arthritis[38]. Six out of 102 cases in our study had circulating antibodies to HCV and 4 were also positive for RF (data not shown). On the other hand, anti-CCP and related autoantibodies do not seem associated with HCV infection[39,40]. Accordingly, only 1 patient with anti-HCV antibodies had anti-CCP, along with RF, in our series.

In conclusion, anti-CCP can be found in a small but significant proportion of patients with a clinical picture of PsA recruited from a tertiary referral center. In these patients anti-CCP are associated with multiple joint involvement and erosive arthritis often requiring DMARD treatment. Further prospective studies are needed to clarify the clinical usefulness of anti-CCP testing in PsA.

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