Acta Derm Venereol 2005; 85: 253–284

Taylor & Francis
Taylor & Francis Group

LETTERS TO THE EDITOR

Anti-citrulline Antibodies in Psoriatic Patients with and without Arthritis

Aurora Parodi[1], Massimo Drosera[1], Bruno Seriolo[2], Loris Barbieri[3] and Alfredo Rebora[1]
[1]*Di.S.E.M Section of Dermatology, University of Genoa, Viale Benedetto XV n. 7 16132 Genoa,* [2]*DIMI Section of Rheumatology University of Genoa, and* [3]*Bouty S.p.A, Milan, Italy. E-mail: aurora.parodi@unige.it*
Accepted August 27, 2004.

Sir,

Psoriatic arthritis (PSA) is a manifestation of psoriasis present in up to 20% of patients with psoriasis. Five variants have been described: asymmetrical acute oligoarthritis, distal interphalangeal joint arthritis, rheumatoid arthritis-like symmetrical polyarthritis (which is the commonest form), spondylitis and arthritis mutilans. In the absence of typical cutaneous or nail lesions, PSA is easily confused with other forms of arthritis, especially rheumatoid arthritis (RA). Recently, antibodies directed to a citrullinated cyclic peptide (anti-CCP) have been proposed as a specific marker for RA (1, 2). We addressed the question as to whether anti-CCP antibodies may help to distinguish PSA from RA.

SUBJECTS AND METHODS

We studied 42 subjects (26 women and 16 men) and 58 controls (40 women and 18 men). Seventeen of the subjects (16 women, 1 man) had rheumatoid arthritis, 2 (men) had seronegative spondylitis, 12 (6 women, 6 men) had the rheumatoid arthritis-like variant of PSA and 11 (3 women, 8 men) had psoriasis without arthritis. Patients with RA were classified according to ARA criteria (3), all of them had polyarticular and symmetrical small joint involvement; eight patients had been classified according to the assessment of functional capacity as belonging to class III and nine to class II. Two of the patients with PSA had cutaneous lesions of erythrodermic psoriasis and 10 psoriasis vulgaris. All the patients with psoriasis without arthritis had psoriasis vulgaris. Of the controls, 15 (13 women, 2 men) had systemic lupus erythematosus (SLE) with non-erosive arthritis, 5 (3 women, 2 men) had SLE without arthritis, 14 (13 women, 1 men) had systemic sclerosis (SSc) with arthralgias, 5 (3 women, 2 men) had SSc without arthralgias, and 8 (women) had Sjögren syndrome. The SLE patients were diagnosed according to the ARA criteria (4).

In all patients, analyses for rheumatoid factor, antinuclear antibodies and anti-CCP antibodies were performed. Rheumatoid factor was measured by agglutination test. Antinuclear antibodies (ANA) were detected using indirect immunofluorescence on HEp 2 cells as substrate; titres of 1/40 were considered positive. Anti-CCP antibodies were detected by quantitative enzyme-linked immunosorbent assay (ELISA) (DIASTAT anti-CCP AXIS-SHIELD Diagnostics Ltd, Dundee, Scotland UK, imported by Bouty S.p.a., Milan, Italy). The wells of the strips were coated with highly purified synthetic peptides containing modified arginine residues (2nd generation test). The cut-off value was 5 U/ml, as recommended by the manufacturer.

RESULTS

Rheumatoid factor was positive in 16 patients with RA, in 1 with PSA, in 5 with SLE and arthritis, in 1 with SSc and arthritis and in 6 with Sjögren syndrome. ANA were positive in 11 patients with RA, 4 with PSA, 4 with psoriasis without arthritis, in all patients with SLE and SSc (with and without arthritis) and in all patients with Sjögren syndrome. In patients with RA, PSA and psoriasis, ANA were present at low titres (1/40). The anti-CCP antibodies were present in 11 patients with RA (65%) (8 belonging to class III and 3 to class II), and in 2 patients without RA, 1 of them having SSc and arthritis and 1 Sjögren syndrome (Table I). None of the psoriatic patients had anti-CCP antibodies.

DISCUSSION

In 1964, a serum antibody directed to a protein component of the keratohyaline granules of buccal mucosa cells, called 'perinuclear factor', was described as very specific for the diagnosis of RA (5). In 1979 another antibody system binding keratin-like structures (using rat oesophagus as substrate) was described in patients with RA; it was named anti-keratin antibody (6). Sebbag et al. (7) showed in 1995 that anti-perinuclear factor and anti-keratin antibodies were directed to the same antigen, the epithelial protein known as filaggrin, an intermediate filament-associated protein involved in the cornification of the epidermis. During cell differentiation,

Table I. *Positivity of immunological tests in relation to diagnosis in 42 patients*

Diagnosis	RA factor	ANA	Anti-CCP antibodies	Total no. of patients
RA	16	11	11	17
Spondylitis	0	0	0	2
PSA	1	4	0	12
Psoriasis	0	4	0	11
SLE+arthritis	5	15	0	15
SLE	0	5	0	5
SSc+arthritis	1	14	1	14
SSc	0	5	0	5
Sjögren syndrome	6	8	1	8

RA, rheumatoid arthritis; ANA, anti-nuclear antibodies; Anti-CCP antibodies, anti-citrullinated cyclic peptide antibodies; PSA, psoriatic arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

 ISSN 0001-5555
DOI: 1080/00015550410024490

filaggrin is dephosphorylated and about 20% of the arginine residues are converted into citrulline by the enzyme peptidylarginine deiminase. Therefore, an ELISA containing synthetic peptides of citrulline was prepared to test anti-filaggrin antibodies, and RA sera were shown to be positive. Although the anti-perinuclear factor and the anti-keratin antibodies were found to be 99% specific, they were never utilized in routine practice, mainly because anti-perinuclear factor could be detected only by indirect immunofluorescence using inconvenient substrates such as oral mucosa cells, and because the anti-keratin antibodies positivity was difficult to read on rat oesophagus (8).

Anti-CCP ELISA is easy to perform and has an excellent specificity and sensitivity (91–98% and 65%, respectively) (1, 2, 8). The anti-CCP antibodies are therefore currently considered very useful for the serological diagnosis of RA, particularly in its early stages. In our study, we found them in 65% of patients with RA and in $<3\%$ of those with other diagnoses (92% specificity and 85% sensitivity). It is interesting that all patients with RA class III had CCP antibodies, i.e. patients with severe disease regularly have these antibodies.

In addition, our data confirm that anti-CCP antibodies are absent in PSA, albeit the number of patients studied was low. Dermatologists should be aware of the usefulness of this test in distinguishing the RA-like variant of PSA from true RA and SLE arthralgias, particularly in the early stages of the diseases or when cutaneous manifestations are not completely developed.

REFERENCES

1. Schellekens GA, de Jong BAW, van den Hoogen FHJ, van de Putte LB, van Venrooij WJ. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. J Clin Invest 1998; 101: 273–281.
2. Schellekens GA, Visser H, de Jong BAW, van den Hoogen FHJ, Hazes JMW, Breedveld FC, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum 2000; 43: 155–163.
3. Arnett FC, Edworthy SM, Block DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315–324.
4. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25: 1271–1277.
5. Nienhuis RLF, Mandena EA. A new serum factor in patients with rheumatoid arthritis. The antiperinuclear factor. Ann Rheum Dis 1964; 23: 302–305.
6. Young BJJ, Mallya RK, Leslie RDG, Clark CJM, Hamblin TJ. Antikeratin antibodies in rheumatoid arthritis. BMJ 1979; 2: 97–99.
7. Sebbag M, Simon M, Vincent C, Masson-Bessière C, Girbal E, Durieux JJ, et al. The perinuclear factor and the socalled antikeratin antibodies are the same rheumatoid arthritis-specific autoantibodies. J Clin Invest 1995; 95: 2672–2679.
8. Van Boekel MAM, Vossenaar ER, van den Hoogen FHJ, van Venrooij WJ. Autoantibody systems in rheumatoid arthritis: specificity, sensitivity and diagnostic value. Arthritis Res 2002; 4: 87–93.

 DOI: 10.1080/00015550510025560