Serological Evaluation of Anti-CCP, ANCA and ANA Autoantibodies in Patients with Psoriasis Vulgaris and Psoriatic Arthritis

Psöriazis Vulgaris ve Psöriatik Artritli Hastalarda Anti-CCP, ANCA ve ANA Otoantikorların Serolojik Değerlendirilmesi

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ABSTRACT Objective: Psoriasis is a chronic, inflammatory and hyperproliferative immune-mediated skin disorder. Psoriatic arthritis is an important comorbidity observed in patients with psoriasis. We aimed to evaluate the importance of some autoantibodies and anti-cyclic citrullinated peptide (-CCP) antibodies in patients with psoriasis vulgaris (PsV) and psoriatic arthritis (PsA), and to contribute to the immunopathogenesis of psoriasis. **Material and Methods:** Forty four PsV and 45 PsA patients, and 32 healthy volunteers were included in the study. Peripheral venous blood samples were collected from patients and healthy volunteers. In serum samples, Anti-CCP antibodies were studied semi-quantitatively, anti-neutrophil cytoplasmic antibody (ANCA) profiles quantitatively with ELISA method, and antinuclear antibody (ANA) profiles were studied quantitatively by immunoblotting. **Results:** Totally 8 (8.9%) patients (2 PsA and 6 PsV) were anti-CCP positive. ANCA positivity was not detected in any of our PsV or PsA patients. A 43-year-old woman with PsA was AMA-M2(+), anti-Ro52(++), anti-nucleosome(+), anti-ds DNA(+). A 38-year-old man with PsV had suspicious anti-nRNP/-Sm positivity (in gray zone); a 33-year-old woman with PsV had anti-SS-A positivity. **Conclusion:** In our study, patients with PsA had less frequent anti-CCP positivity compared to the present data in the literature. ANCA positivity was not detected in any of our patients. ANA profile antibodies were detected only in three patients. Consequently, it is thought that larger scale, multicentered studies are needed in order to enlighten the role of anti-CCP antibodies and other autoantibodies in the immunopathogenesis of psoariasis and psoriatic arthritis.

Key Words: Autoantibodies; arthritis, psoriatic

ÖZET Amaç: Psöriazis kronik, inflamatuvar ve hiperproliferatif immün aracılı bir deri hastalığıdır. Psöriatik artrit ise psöriazis hastalarında gözlenen önemli bir komorbiditedir. Biz de çalışmamızda Psöriazis Vulgaris (PsV) ve Psöriatik Artrit (PsA) hastalarında anti-siklik sitrilün peptid (anti-cyclic citrullinated peptide: anti-CCP) ve bazı otoantikorların önemini değerlendirmeyi, psöriazis immünpatogenezinin aydınlatılmasına katkıda bulunmayı amaçladık. **Gereç ve Yöntemler:** Çalışmaya 44 PsV ve 45 PsA hastası ile 32 sağlıklı gönüllü dâhil edildi. Anti-CCP antikoru semi-kantitatif olarak ve anti-nötrofil sitoplazmik antikor (ANCA) profili de kantitatif olarak ELISA metoduyla değerlendirildi. Antinükleer antikor (ANA) profili ise immünblot yöntemi ile kantitatif olarak çalışıldı. **Bulgular:** Toplam 8 (%8,9) hastada (2 PsA hastası ve 6 PsV hastası olmak üzere) anti-CCP pozitif olarak tespit edildi. PsV ve PsA hastalarından hiçbirinde ANCA pozitifliği saptanmadı. Kırk üç yaşında PsA'li bir bayan hastada AMA-M2(+), anti-Ro52(++), anti-nucleosome(+), anti-ds DNA(+) idi. Otuz sekiz yaşında PsV'li erkek hastada şüpheli anti-nRNP/-Sm pozitifliği vardı. Otuz üç yaşında PsV'li bir bayan hastada ise anti-SS-A pozitifti. **Sonuç:** Çalışmamızda PsA'lı hastalarda literatürdeki mevcut verilere göre daha az sıklıkla anti-CCP pozitifliği görüldü. ANCA pozitifliği hastaların hiçbirinde saptanmadı. ANA profil antikor pozitifliği ise sadece üç hastada saptandı. Sonuç olarak psöriazis ve psöriatik artrit immünopatogenezinde anti-CCP ve diğer otoimmün antikorların rolünü araştırmak için daha büyük çapta, çok merkezli çalışmalara ihtiyaç olduğu düşünüldü.

Anahtar Kelimeler: Otoantikorlar; artrit, psöriatik

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Psoriasis is a chronic, inflammatory and hyperproliferative skin disease with a genetic basis.[1] The knowledge gained over the past 3 decades lets us postulate that psoriasis is an immunologically induced disease in which various cells play a dominant role at different stages.[1] Psoriatic arthritis (PsA) has been classically defined as an inflammatory arthritis associated with psoriasis that shares many features of rheumatoid arthritis (RA).[2,3] Therefore, it is very difficult to make a differential diagnosis between PsA and RA in a patient with psoriasis.[3] In comparison with other relevant inflammatory arthropathies, in which a definite diagnosis is frequently possible only by means of laboratory investigations, in PsA true laboratory diagnostic markers are lacking.[2] However, in a more accurate approach, laboratory investigations may offer important additional tools to better interpret the various and heterogenous spectrum of the disease expression of PsA. Laboratory investigations may be used to obtain information in the fields of diagnosis, disease activity, prognosis and evaluation of the effects of therapy.

Citrulline is a deaminated and post-translationally modified derivative of arginine.[4] The transition from arginine to citrulline is catalyzed by peptidylarginine-deiminase (PAD) that has five isoforms in mammals.[4] Tissue citrullination is a physiological process underlying epithelial keratinization, inflammation and increased apoptosis which are also very important processes in the pathogenesis of psoriasis.[5] There is relatively small amount of citrullinated proteins in the normal synovial tissue, whereas active citrullination has been associated with synovitis.[6] Citrullinated protein epitopes have been identified in extravascular fibrin deposits and extracellular fibrinogen aggregates within the RA synovium.[7] Filaggrin, the first citrullinated protein identified, as potential autoantigen in RA is an epidermal protein that is usually absent in the synovium.[8] Thus, other citrullinated proteins, such as fibrin or vimentin that are abundantly expressed and citrullinated in synovial tissues may drive autoantibody production.[9] These autoantigens induce the production of anti-citrullinated protein/peptide (anti-CCP) autoantibodies that have been associated with autoimmunity underlying RA.[10] The group of anti-CCP antibodies has also been referred to as anti-filaggrin antibodies previously.[7] Since the pathogenesis of psoariasis is highly associated with inflammation and fibrin formation, we proposed that these citrullinnated proteins might be important autoantigens in the unknown etiopathogenesis of psoriasis and psoriatic arthritis also.

Although most studies suggest high diagnostic specificity and sensitivity of anti-CCP antibodies in RA tissue, citrullination and anti-CCP production have been detected in patients with other types of arthritis, but less frequently.[5,6,11-13] Besides, anti-CCP titer has been shown to be an early prognostic marker to predict RA.[14] There is also a growing interest regarding the prevalence and clinical importance of anti-CCP antibodies in PsA.[12] In addition to being useful in diagnosis, anti-CCP antibodies might be an indicator of prognosis and disease severity in PsA as in RA. Recently, some clinical trials have revealed the presence of anti-CCP in PsA patients in 5.6-15.7%.[15] Although anti-CCP antibodies are highly specific for RA, their role in PsA remains unclear.[16]

Etiopathogenesis of psoriasis has not been completely understood. The presence of autoantibodies was reported in psoriasis patients without any clinical symptoms.[17] Many autoimmune diseases have been reported to be associated with psoriasis such as RA, systemic lupus erythematosus (SLE), scleroderma, mixed connective tissue disease (MCTD), autoimmune thyroiditis, pernicious anemia, Sjogren's syndrome, and myasthenia gravis.[11] In this study, we aimed to investigate anti-CCP antibodies in patients with PsV and PsA, and hoped to contribute to the knowledge in immunopathogenesis of psoriasis. Since the triggering antigen in the proposed immunological mechanisms of psoriasis have not been completely understood yet, we investigated anti-neutrophil cytoplasmic antibody (ANCA) and antinuclear antibody (ANA) in addition to anti-CCP to search for other probable triggering antigens as well as trying to exclude other inflammatory connective tissue diseases like SLE and MCTD that could be associated with psoriasis in our cases.

MATERIAL AND METHODS

A total of 89 (39 males, 50 females) patients participated in this study. Forty four PsV (19 males, 25 females) and 45 PsA (20 males, 25 females) patients who had applied to dermatology and/or rheumatology clinics of Gazi University Hospital and to the rheumatology clinic of Baskent University Hospital being diagnosed with psoriasis clinically and histopalogically were included in this study. Thirty two healthy (15 males, 17 females) volunteers who had neither psoriasis vulgaris, psoriatic arthritis nor any known autoimmune or inflammatory diseases were taken into the healthy control group. Date of the Human ethics committee approval is 27 November 2006, and approval number is 341 for this study. Patients and the members of the healthy control group were informed prior to the study, and signed disclosure forms. Psoriasis patients with a defined arthritis related to a known autoimmune disease, e.g. rheumatoid arthritis (but not PsA), patients with positive rheumatoid factor (RF) test result, and patients who had taken long term TNF-α treatment were excluded from the study. None of the healthy volunteers had RF positivity either. Patients were grouped according to psoriasis area and severity index (PASI) scoring criteria: PASI scores ≤10 were evaluated as mild, 10-20 were evaluated as moderate, ≥20 were evaluated as severe disease. Peripheral venous blood samples were collected and centrifuged at 3000xg for 15 minutes. Isolated serum samples were kept at -20°C until the assay day. In serum samples, anti-CCP antibodies were studied semi-quantitatively with a commercial ELISA kit (anti-CCP ELISA, IgG, Euroimmun, Lübeck Germany) and autoantibody titers in serum samples are calculated using titers of known standards supplied in the kit by means of a computer-based statistics program called Microsta. As an additional laboratory parameter, we determined ANCA and ANA profiles in our study group.

ANCA Profile [*anti-proteinase 3 (PR3), anti-myeloperoxidase (MPO), anti-elastase, anti-lactoferrin, anti-catepsin G, Bactericidal/permeability-increasing protein (BPI), ANCA mixture*] was studied qualitatively with a commercially available ELISA kit (ANCA Profile ELISA, IgG, Euroimmun). ANA profile [*anti-SS-A (anti-Ro), anti-SS-B (anti-La), anti-Ro52, anti-Sm, anti-nRNP/Sm, anti-Scl 70, anti-PM-Scl, anti-Jo1, anti-centromer protein B, anti-dsDNA, anti-histone antibody, anti-ribosomal P protein, anti-nucleosome antibody, anti-mitochondrial antibody-AMA-2*] was studied with a commercial immunoblotting assay (ANA Profile 3, IgG, EUROLINE, Euroimmun) where anti-Sm stands for anti-Smith antigen, anti-nRNP for anti-nuclear ribonucleoprotein, anti-Scl for anti-scleroderma, anti-PM for anti-polymyositis. The results were assessed qualitatively visually as well as digitally using EUROLINE Scan program.

STATISTICAL ANALYSIS

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). While continuous variables were shown as mean±standard deviation, otherwise, number of cases and (%) was used for nominal data. The mean differences between groups were compared by Student's t test. Nominal data were evaluated by Pearson's Chi-square or Fisher's exact test; where appropriate. A p value less than 0.05 was considered statistically significant.

RESULTS

In the study group, 39 (43.82%) were males and 50 (56.17%) were females. The mean age was 46.7±13.5 (19-78) years. In the healthy control group, 15 (46.87%) were males and 17 (%53.13) were females; the mean age of this group was 37.7±11.6 (18-64) years (Table 1). While there was no statistically significant difference between groups regarding for gender distribution (p=0.766), the mean age in study group was statistically significantly

TABLE 1: Demographical data of the groups.

Variables	Control group (n:32)	Patients (n:89)	p-value
Age (years)	37.7±11.6	46.7±13.5	<0.001
Minimum-maximum ages (years)	18-64	19-78	
Gender			0.766
Male	15 (46.9%)	39 (43.8%)	
Female	17 (53.1%)	50 (56.2%)	

higher than the healthy control group (p<0.001). However this difference had no effects on the parameters of this study. According to dermatological examination including PASI scoring, 63 (70%) patients with PsV had mild, 17 (19%) had moderate and 9 (10%) had severe disease, while in PsA patients 27 (79%) had mild, 6 (18%) had moderate and 1 (3%) had severe disease. Anti-CCP antibodies were high-positive (>10 Relative Units-RU/mL) in 5 patients and was low-positive (5-10 RU/mL) in 3 patients. That is, sum of 8 (8.9%) patients were detected as anti-CCP positive and 2 of these 8 patients had psoriatic arthritis.

None of the patients in our study group had ANCA positivity. When ANA profile was evaluated: a 43-year-old female patient with PsA was AMA-M2(+), anti-Ro52(++), anti-nucleosome (+), anti-ds DNA(+); a 38-year-old male PsV patient (without PsA) had suspicious (gray zone) anti-nRNP/-Sm positivity; a 33-year-old female PsV patient had anti-SS-A (++) (Table 2). We did not detect anti-CCP, ANCA or ANA positivity in the healthy control group.

DISCUSSION

In our study, anti-CCP antibodies were high- positive in 5 patients and low -positive in 3 patients. In total, 8 (8.9%) patients were detected as positive and 2 (5.8%) of these 8 patients had psoriatic arthritis. In a study by Alenius et al., anti-CCP antibodies were found to be more prevalent in patients with PsA than in patients without arthritis.[11] After 4-year follow-up, most of these patients fulfilled theAmerican College of Rheumatology (ACR) criteria for RA. Both PsA and RA are quite common in the population, so there is a possibility that the patients have both PsA and RA. These data shows the complexity in differential diagnosis between the two diseases. Contrary to the results of Alenius et al., we found out that 13.6% of psoriasis patients without PsA were positive for anti-CCP antibodies.[11] Alenius group had investigated rheumatoid factor (RF) and erythrocyte sedimentation rate, but did not perform PASI scoring and did not assay for ANA and ANCA autoimmune antibodies; they reported that patients with PsA positive for anti-CCP antibodies more often had polyarthritic disease.[11]

Abdel Fattah et al. tested 40 PsA, 40 psoriasis without arthritis, 40 RA and 40 healthy controls for anti-CCP antibodies, and found that anti-CCP positivity was 17.5% in PsA and 85% in RA patients in their study group. Peripheral and axial joint evaluation was performed according to Moll and Wright criteria, modified by Helliwell et al.[18] No statistically significant differences were found between different groups regarding their age and gender. In our study, the female/male ratio was found to be 1.43/1 in the PsA group; however female/male ratio was 0.91/1 in PsV patients who had no arthritis and who were not suffering from joint pain. When psoriasis patients with and without arthritis were assessed regarding to age, gender, disease duration and PASI scoring, no statistically

TABLE 2: Autoantibody positivity in different groups.

	Control group	Patient groups			
Variables	(n:32)	PsA (n:45)	PsV (n:44)	Total (n:89)	p-value
Anti-CCP	-	2 (4.4%)	6 (13.6%)	8 (9.0%)	0.108
ANA	-	-	-	1 (1.1%)	-
AMA-M2	-	1 (2.2%)	-	1 (1.1%)	-
Anti-Ro52	-	1 (2.2%)	-	1 (1.1%)	-
Anti-Nucleosome	-	1 (2.2%)	-	1 (1.1%)	-
Anti-DS-DNA	-	1 (2.2%)	-	1 (1.1%)	-
Anti-nRNP/-Sm	-	-	1 (2.3%)	1 (1.1%)	-
Anti-SS-A	-	-	1 (2.3%)	1 (1.1%)	-
ANCA	-	-	-		-

significant difference were observed between the groups.[3] We observed mild psoriasis in 57.7% of PsV patients without PsA and in 79% of PsA patients. This can be related to the fact that PsA patients take systemic treatment much more commonly compared to PsV patients as well as to the slight personal differences in evaluation of the patients by physicians. In their conclusion Abdel Fattah et al. reported that anti-CCP-positive PsA patients might suffer from an overlap with a preclinical form of RA and in such cases anti-CCP testing could help in selection of patients who might need follow-up, especially withAmerican Rheumatism Association (ARA) criteria.[3]

Maejima et al. examined anti-CCP in 15 patients with PsA, and compared with 18 control patients who had other types of psoriasis.[19] Similar to our results, there were no significant differences in PASI scores, duration of illness, sedimentation and CRP levels among patients with and without anti-CCP positivity. Three PsA patients were positive for anti-CCP, but none of the control patients gave positive results.[19] The presence of anti-CCP in PsA patients may indicate that they will develop jsevere joint disease.[20] This suggests that anti-CCP would be a marker of disease severity.

Shibata et al. evaluated 16 PsA, 15 psoriasis, 9 RA patients and 11 healthy controls. Unlike our study, they detected high titers of RF positivity and anti-CCP positivity in 13% of PsA patients.[21]

In a recent paper by Helliwell et al. reporting the results of the Classification criteria for Psoriatic Arthritis (CASPAR) study, anti-CCPs were detected in 26/588 patients with PsA, 15/388 with polyarticular variety and 11/200 with non-polyarticular PsA.[18] These data, indicating that the occurrence of anti-CCP was not limited to the polyarthritis, confirmed those reported by another recent study by Bogliolo et al. They examined 102 PsA patients and found anti-CCP positivity in 16 patients who were mostly affected with symmetric polyarthritis. In this population, 19/102 patients had RF and anti-CCP was present in 11 of them. Thus in PsA, the presence of anti-CCP was not restricted to those with clinical pictures resembling RA, and therefore it seemed to be unreliable as a marker of RA. However, as in RA, the presence of anti-CCP was associated with an increased number of erosions, probably reflecting a more severe outcome.[20] Dalmády et al. investigated the prevalence of anti-MCVs (mutated citrullinated vimentin) in PsA and PsO (psoriasis without joint symptoms).[22] They found that the anti-MCV levels in the PsA patients were significantly higher than those in the PsO group. Their results suggest that anti-MCVs can be used as novel markers in the diagnosis of PsA and in a subset of PsO patients.

Rosenberg et al. reported that they found granulocyte-specific ANA in 7 of 52 PsA cases, but not in any of other psoriasis patients.[23] ANA was positive in one patient with psoriasis. These results are parallel to our findings. In our study, a 43-year-old female patient with PsA was AMA-M2(+), anti-Ro52(++), anti-nucleosome (+), anti-ds DNA(+); a 38-year-old male patient with PsV but not PsA, had a suspicious (gray zone) anti-nRNP/-Sm positivity; a 33-year-old female patient with PsV was positive for anti-SS-A. AMA-M2 positivity is generally thought to be associated with chronic liver diseases or hepatitis B carrier state. On the other hand, anti-Ro-52, anti-dsDNA and anti-nucleosome positivity suggest that this patient must be evaluated in terms of SLE-like in the study of Zalla and Muller.[24]

Zalla and Muller identified 42 cases of SLE among 9400 psoriasis patients in a 10-year retrospective study, with prevalence of SLE in 0.69%.[24] Although our patient who was anti-dsDNA positive had no clinical evidence of SLE yet, we decided that she should be taken into follow-up for a possible SLE in the future.

Anti-nRNP seropositivity is seen with a high frequency in patients with mixed connective tissue disease. In our study, a 38-year-old male patient with PsV without arthritis had suspicious anti-nRNP positivity in repeated assays; therefore, we took him under follow-up for a probable mixed connective tissue disease in the future.

Singh et al. studied a total of 118 psoriasis patients in order to find the prevalence of various au-

toantibodies in psoriasis patients and its correlation with gender, age, and type.[25] RF, anti-dsDNA, ANA and anti-thyroid microsomal antibodies (TMA) were studied. Psoriasis patients included 75 cases (63.6%) of plaque psoriasis, 27 cases (22.9%) of palmoplantar, 6 cases (5.1%) of psoriatic erythroderma, 4 cases (3.4%) of psoriatic arthritis, and 3 cases (2.5%) guttate psoriasis. A total of 34 (28.8%) cases of psoriasis were found to be positive for at least one of the autoantibodies. ANA positivity was more frequent among males (57.1 vs. 42.9%) whereas anti-TMA positivity was more frequent in females (66.7 vs. 33.3%).[25] It was concluded that either these autoantibodies were found to be present in psoriasis patients or latent autoimmune diseases developed in psoriasis patients without any clinical symptoms. Only one female patient was positive for anti-dsDNA in our study group, and we took her under follow-up for a possible SLE in the future.

Antonelli et al. tested thyroid autoimmunity in PsA patients, and reported that 28% of his patients were positive for anti-TMA.[26]

Kutukculer et al. analyzed various autoantibodies in patients with psoriasis, and reported that 5.8% of cases were positive for RF, only one case was positive for ANA and dsDNA.[27] Similar to their results, only a 33-year-old female PsA patient was found to be anti-SS-A positive in our study. They found P-ANCA positivity in 33.3% of their patients and reported that the results of their study had supported autoimmunity in the pathogenesis of psoriasis vulgaris while none of our patients had ANCA seropositivity.

Janjumratsang et al. investigated some immunological parameters [ANA, anti-dsDNA, anti-Ro and anti-nuclear ribonucleoprotein (nRNP)] in psoriasis patients using direct immunofluorescence.[17] Of 300 cases comprising 189 men (62.9%) and 111 women (37.1%), 17 (5.7%; 10 men, seven women) were positive for at least one of these immunological parameters.[17]

The exact cause of autoimmunity in psoriasis is not clear. Atassi and Casali reported that it might be due to the overlapping of the locations of some potent autoimmune genes and psoriasis genes.[28] Alteration in self-tolerant proteins may also elicit autoimmune responses or molecular mimicry is supposed to be one of the causes for autoimmunity, due to the structural similarity between streptococcal M protein with keratin 17 protein of skin.[29,30]

In conclusion, patients with PsA had less frequent anti-CCP positivity compared to the present data in the literature in our study. ANCA positivity was not detected in any of our patients. Only one female patient with PsA was AMA-M2(+), anti-Ro52(++), anti-nucleosome (+), anti-ds DNA(+); one male PsV patient had suspicious anti-nRNP/-Sm positivity, and one female PV patient was positive for anti-SS-A. Consequently, it seems that larger scale and multicentered studies are needed in order to enlighten the role of anti-CCP antibodies and other autoantibodies in the immunopathogenesis of psoariasis and psoriatic arthritis.

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