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Anti- Modified Citrullinated Vimentin Antibody Levels in Psoriasis Patients

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Abstract

Background: Being one of the antibodies against citrullinated proteins/peptides (ACPA), anti-mutated citrullinated vimentin (anti-MCV) is specific for the diagnosis of rheumatoid arthritis (RA). Additionally, high anti-MCV levels were detected in some arthritis related diseases. There are limited reported data about ACPAs in patients with psoriatic arthritis (PsA). To our knowledge, only one study has examined anti-MCV antibodies in psoriasis which shares common etiopathogenesis with PsA. The aim of this study was to investigate the role of anti-MCV antibodies in psoriasis and PsA pathogenesis.

Material and Methods: Serum anti-MCV levels were measured in 28 patients with psoriasis; 21 patients with PsA and 28 healty contols by enzyme-linked immunosorbent assay. We correlated anti-MCV levels with disease duration, Psoriasis Area and Severity Index (PASI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), clinical variables, treatment courses and smoking habits.

Results: The median titers of anti-MCV antibodies were 36.16 U / ml (0.99- 136.62 U / mL) in psoriasis group, 89.54 U / mL (5.39 - 907.44) in PsA group and 39.07 U / mL (2.41 - 391.08) in the control group. The Anti-MCV levels were significantly higher in patients with PsA than patients with psoriasis (p = 0.003). Although it was not statistically significant, anti-MCV levels were higher in patients with PsA than those in control group (p = 0.065). There were no significant correlation of anti-MCV levels with disease durations, disease activity variables, nail involvement, and treatment courses.

Conclusion: Anti-MCV antibodies are not related with the disease duration, severity or treatment modalities. Our results show that anti-MCV antibodies has not a role in the pathogenesis of psoriasis. Anti- MCV antibodies might have a role in the development of arthritis in psoriasis as the anti-MCV levels were significantly higher in patients with PsA than patients with psoriasis. Future researchs are needed to show the definite role of anti-MCV in pathogenesis of psoriasis and PsA and clinical importance of this marker.

Introduction

Vimentin is the intermediate filament of the mesenchymal cells that has been shown to play a role in the mechanical stability, motility and migration of these cells [**1,2**] Vimentin-expressing epithelial cells have been shown to be flatter than those of keratin expressing only, and flat cells are less susceptible to friction stress. Vimentin-induced cell flattening can give epithelial cells the ability to resist various external mechanical forces [**3**].

Pituitary tumor transforming gene 2 (PTTG2) was observed to be more expressed in psoriatic cells than normal cells. It is thought that overexpression of this gene may decrease the expression of e-cadherin and increase vimentin expression, increasing the epithelial-mesenchymal transition abnormally and causing psoriasis [**4**] In some previous studies, it has been shown that e-cadherin expression in the granular, upper spinous and basal layers of psoriatic skin is reduced [**5**] Vimentin is also present in synovium and fibroblast-like synoviocytes and plays an important role in endothelial cell resistance to mechanical stress [**6**].

Vimentin is expressed on activated macrophages by means of TNF-alpha induced vimentin secretion. Vimentin cannot be citrullinized in vivo, citrullination occurs in macrophages or neutrophils during inflammation, apoptosis and cellular differentiation by posttranslational modification which is carried out by the peptidyl arginine deaminase (PAD) [**7,8**] The level of citrullinated proteins reaches higher levels in inflamed tissues [**9**]. Other citrullinated peptides are filaggrin, type II collagen, α-enolase, and fibrinogen [**8**]. When a large number of citrulline is present in the structure of these proteins, they are perceived as foreign by immunity. Antibodies targeting them are triggered by the effects of genetic and environmental factors, and named as anti-citrullinated protein / peptide antibodies (ACPA) [**9**].

Antibodies to citrullinated vimentin is called anti-mutated citrullinated vimentin (anti-MCV) and detected by an ELISA system that contains genetically modified, mutated citrullinated vimentin (MCV) as antigen to improve the performance of the test. Anti-MCV antibodies in patients with RA is thought to be produced due to the insufficient clearance of apoptotic materials [**10**]. Anti-MCV is included in the ACPA group and it is a more sensitive but less specific marker than anti-cyclic citrullinated vimentin (anti-CCP) for the diagnosis of RA. [**1**].

High concentration of anti-MCV and ACPAs were detected in synovial fluid and peripheral circulation of patients with RA [**11**], however lower levels of them have also been found in synovium [**12**] and in serum of the patients with PsA [**13,14**]. Psoriatic arthritis (PsA) is a seronegative inflammatory arthritis which develops in up to 30 percent of patients with psoriasis [**15**]. It is characterized by a negative rheumatoid factor (RF) and has different clinical phenotypes including distal, oligoarticular, polyarticular, primarily axial and arthritis mutilans [**16**]. Some clinical presentations of PsA, especially the severe, erosive and symmetrical polyarthritis, are similar to those of RA, in a manner of making it difficult to distinguish [**17,18**].

The specificity and sensitivity of anti-MCV antibodies for other arthritic diseases is low compared with RA [**19**]. There are recent reports describing the frequency of ACPAs in PsA and psoriasis [**20,14**]. The presence of anti-MCV antibodies in psoriasis and PsA patients has been studied by Damjanovska et al, who showed that anti-MCV levels in PsA patients were significantly higher than those in psoriasis group [**13**]. The present study aimed to examine the presence of anti-MCV antibodies in psoriatic patients with and without manifestation of joint inflammation and to further assess its clinical value.

Methods

Patients

Twenty-eight patients with psoriasis (16 males, 12 females) who were diagnosed clinically and pathologically at the dermatology department and 21 patients (7 males, 14 females) with PsA who were followed simultaneously by rheumatology and dermatology departments were included in the study. The study was reviewed by the ethics committee and informed consent was obtained from all patients.

The dermatological examination of the patients included in the study was performed by the same physician (GC), and besides demographics, the following data were collected: duration of psoriasis, duration of arthritis, current treatment, smoking habits (**Table 1**).

The diagnosis of the patients in the PsA group was made by an experienced rheumatologist according to CASPAR criteria and the disease activity was evaluated by the same physician. Physical examinations included severity of psoriasis (assessed with the Psoriasis Area and Severity Index) and and nail involvement. BASDAI was used for the arthritic disease activity.

Table 1. The Relationship Between Smoking and Anti-MCV Levels in Psoriasis PsA and Control Groups

	Anti-MCV median (min-max)	P
Psoriasis /smoking+	33,03 (2,16 -99,46)	0,532
Psoriasis /smoking -	37,09 (0,99- 136,63)	
PsA /smoking +	43,11 (5,40- 274,96)	0,340
PsA /smoking -	96,78 (31,04- 907,44)	
Control /smoking +	129,32 (19,99- 252,33)	0,030
Control /smoking -	34,73 (2,41- 391,09)	

Laboratory Methods

Venous blood samples were taken from patients after fasting 8-12 hours. Serum samples centrifuged at 3000 rpm for 10 minutes were placed in separate ependorfs and stored at -80 ° C until the day of analysis. On the day of the analysis, serum samples extracted according to the manufacturer's instructions were kept at room temperature (18 - 25 ° C) for 30 minutes and studied at the Biochemistry Clinic. Anti-MCV antibodies were measured by ELISA, using anti-MCV ELISA kit (Orgentec Diagnostika GmbH, Mainz, Germany).

Statistical Analysis

Data were analyzed using SPSS for Windows 15 package program. Descriptive statistics were presented as mean ± standard deviation for variables with normal distribution; median (min - max) for non-normal variables; and number of cases and % for nominal variables. The significance of the difference of two groups were investigated by t-test or ANOVA and medians were performed by Mann Whitney U or Kruskal Wallis tests as indicated in tables. Nominal variables were evaluated by Pearson's chi square or Fisher exact test. Spearman's rank correlation was used to test for correlations between continuous variables in small samples. Statistical significance is set at $P<0.05$.

Results

The study included 28 patients with psoriasis without joint involvemen (psoriasis group), 21 with psoriatic arthritis besides psoriasis (PsA group) and 28 healty controls. All of the patients in psoriasis group had plaque type psoriasis. Of them, 16 (57.1%) were men and 12 were women (42.9%). PsA group was included 7 (33.3%) men and 14 (66.7%) women. In the control group, there were 13 (46.4%) men and 15 (53.6%) women. The mean age was 46,04 ± 13,2 (23-65) in psoriasis group; and 48.7 ± 10.2 (27-65 in PsA group; and 46.5 ± 13.3 (18-65) in control group. Three groups were similar on the base of age and gender. The demographic and clinical characteristics of the groups were presented in (**Table 2**).

Table 2. Demographic and Clinical Teatures of Psoriasis, PsA and Control Group

	PsA		**Psoriasis**	**Control**
Gender (m/w)	7/14		16/12	13/15
Age (mean)	48,7±10,2		46,0±13,2	46,5±13,3
Psoriasis duration (month) median (min-max)	144 (24-360)		168 (3-492)	-
Arthritis duration (month) median (min-max)	30 (6-192)		-	-
Smoking habit(%)	42,9		53,6	21,4
Clinical types of Psoriasis and PsA	Polyarthicular	9 (42,9)	All of the patients had psoriasis vulgaris	-
	Oligoarthicular	6 (28,6)		
	DIP ınvolvement	2 (%9,5)		
	Spondiloarthritis	4 (%19)		
PASI median (min-max)	4 (0-13,2)		5 (0-20)	-
BASDAI median(min-max)	3,8 (1,4-7,4)		-	-
Treatment situation	No systemic treatment: 7		No systemic treatent: 8	
	DMARD: 12		Conventional :10	
	Biologic: 2		Biologic: 10	

The median titer of anti-MCV antibodies was 36.16 U / ml (0.99- 136.62 U / mL) in psoriasis group; and 89.54 U / mL (5.39 - 907.44) in PsA group; and 39.07 (2.41 - 391.08 U / mL) in the control group (**Table 3**). Anti-MCV levels were significantly higher in the PsA group than in the psoriasis group (p = 0.003) (**Table 4**) (**Figure 1**).

When psoriasis, PsA and control groups were compared in terms of smoking prevelance (**Table 2**), it was significantly higher in the psoriasis group than the control group (p = 0.027). No association was observed between anti-MCV antibody levels and presence of smoking in psoriasis and PsA group (p=0.523 and p=0.340, respectively). However, serum anti-MCV levels exerted moderate positive correlation with smoking habits in the control group (r = 0.41, p = 0.03) (**Table 1**).

Median disease duration of psoriasis was 156 (3-492) months and the median disease duration of arthritis was 30 (6-192) months. There was no correlation between disease duration and anti-MCV levels in Psoriasis (p=0,961) or in PsA groups (p=0,628).

The median of the PASI scores were 4 (0-13.2) in psoriasis group; 5 (0-20) in PsA group; and the median of the BASDAI scores was 3.8 (1.4- 7.4) in patients with arthritis. There were no correlation between the titres of anti-MCV antibodies and PASI scores, either in the patients with psoriasis or PsA (p = 0.989). Similarly, no significant correlation was found between the BASDAI scores and anti-MCV antibody levels of patients with PsA (p = 0.312).

There was no mutated arthritis among the patients with PsA. Anti-MCV levels were similar in those groups divided according to types of joint involvement (p = 0.18).

There was no statistically significant relationship between the treatment status of patients and anti-MCV antibody levels in PsA (p = 0.330) (Figure 7) or in psoriasis groups (p = 0.126) (Figure 8). Additionally, no association was observed between anti-MCV levels and presence of nail involvement (p>0.05).

Conclusıons

Citrullinated vimentin targetted antibodies are the member of the family of reactive autoantibodies to citrullined proteins and are considered as one of the most specific serological markers for the diagnosis of RA. In the literature, these antibodies were detected in systemic lupus erythematosus (SLE) [**21**]. systemic sclerosis [**22**]. Familial Mediterranean Fever [**23**]. and primary biliary cirrhosis [**24**]. Gilliam et al. demonstrated that anti-MCV elevation was observed especially in the polyarticular and oligoarticular involvement of juvenile idiopathic arthritis [**25**]. Following studies have shown that anti-MCV can be detected in spondiloarthropaties [**26**]. In a recent study, 15% of PsA and 14% of ankylosing spondilitis (AS) patients were positive for anti-MCV [**19**]. PsA is a joint-destructive psoriasis-related inflammatory arthritis in which rheumatoid factor is typically absent. Psoriasis is a chronic inflammatory disease in which T cell mediated immune response is thought to play a role in the pathogenesis, but other elements of the immune system and keratinocytes are also involved [**27,28**]. PsA mostly occurs during the course of psoriasis; it is a chronic inflammatory arthritis with different clinical presentations, so-

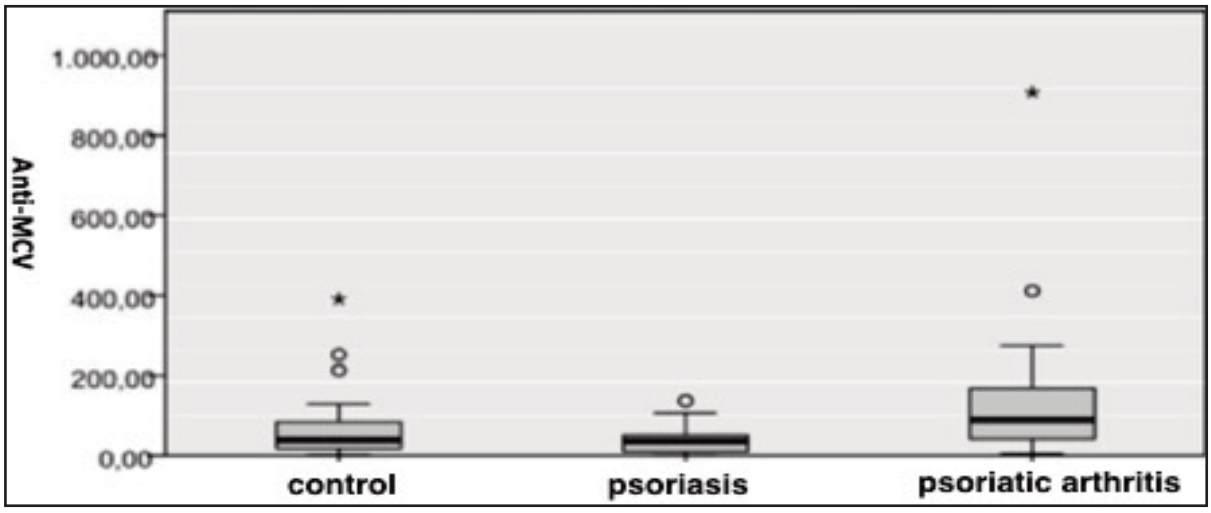

Figure 1. Anti-MCV levels of Psoriasis, PsA and Control Groups

Table 3. Anti-MCV Antibody Titers in Psoriasis, PsA and Control Groups

	Median(U/ml)	Min-Max (U/ml)
Psoriasis (n=28)	36,16	0,99-136,62
PsA (n=21)	89,54	5,39-907,44
Control (n=28)	39,07	2,41-391,08

metimes interfering with RA. Disease severity, widespread involvement, and especially nail involvement are considered as risk factors for the development of arthritis in patients with psoriasis [**29**].

It is known that T-cell mediated immunity plays a role in the pathogenesis of both psoriasis and PsA [**30**]. When we consider these diseases histopathologically, common findings such as dilated veins and perivascular mononuclear cell infiltration are noteworthy in synovium and psoriatic skin histopathology [**31**]. However, oligoclonal T cell patterns and the antigens recognized by them have been identified differently over the skin and synovium. After injection of human T lymphocytes taken from psoriatic skin to immuncompromised and human skin grafted mice; psoriatic lesions occurred but no arthritis developed [**32**]. While psoriasis and PsA are undoubtedly related; the overlap and distinction between their pathogenesis is not completely clear [**33**].

Citrullinated proteins and antibodies against them are thought to play a role in the pathogenesis of inflammatory processes involving arthritis [**9**]. Citrullinated filaggrin, type II collagen, α-enolase, fibrinogen and vimentin have been detected immunohistochemically to be accumulated in different forms of arthritis [**8**]. Antibodies targetted to these proteins are commonly referred to as ACPA and have been studied in detail in RA but limited data are available in PsA [**9**] [**13**]. Although it is higher in rheumatoid arthritis; in psoriatic arthritis synovium and in the peripheral circulation of patients, there is also submicron extracellular vesicles called microparticles. These vesicles are formed during apoptosis or activation processes of platelet and neutrophils. Proteins such as fibrinogen and vimentin are expressed on the surface of these microvesicles [**34**]. In RA, it has been shown that citrullination of these proteins cause formation of autoantibodies in synovial fluid, and these antibodies also form immune complexes with high proinflammatory activity. The binding of ACPA to its target on the microparticle is thought to enhance the formation of microparticle immune complexes (MPICs), and immune complex formations are believed to sustain inflammation. In PsA, it was stated that these microparticles carry less immune complexes , are smaller in size and have a lower proinflammatory property than RA [**35**].

It is not clear whether platelet and leukocyte-derived MPICs are formed in peripheral circulation or in synovial fluid. The functions of microparticles, shown in autoantibody related rheumatic diseases such as RA and SLE, include stimulating immune system, inducing release of cytokines and leukotrienes, stimulating matrix metalloproteinase production, forming immune complexes, contributing to thrombotic susceptibility and endothelial activation. These proinflammatory effects may lead to the formation of synovitis [**36**]. Anti-MCV antibodies were investigated in patients with psoriasis and PsA based on this inflammatory mechanisms. There are a number of studies in the literature investigating Anti-MCV and other ACPAs in PsA and psoriasis [**13,14**] [**20,37**].

Table 4. Comparison of Anti-MCV Antibody Levels Between Groups

	Psoriasis	PsA	Control
Psoriasis		0,003	0,896
PsA	0,003		0,065
Control	0,896	0,065	

Dalmady et al. have investigated the correlation between antibody titers and clinical laboratory findings on 46 patients with PsA and 42 patients with psoriasis. As a result of this study, anti-MCV levels were found to be significantly higher in patients with PsA than in patients with psoriasis and control group [**13**]. In our study, the level of anti-MCV antibody was significantly higher in patients with PsA than in patients with psoriasis in parallel with the findings of Dalmady et al. In contrast to the study of Dalmady et al., there was no significant difference between either of the two patients group and the control group. However, there was more than 2-fold difference between the median value of PsA patients and control group, and this difference was close to the limit of statistically significance (p=0,065). Therefore, we think that the statistically significant difference can be obtained in larger patient and control groups. Dalmady et al. found that anti-MCV levels in psoriasis group were statistically significantly higher in patients with moderate to severe disease than those with mild disease [**13**]. However, we did not find any significant correlation of PASI scores and anti-MCV antibody levels. Although we have used a different scoring system for the severity of the disease; similar to the results of that study, we found no significant correlation between anti-MCV antibodies and disease severity in patients with PsA. There was no statistically significant relationship between disease duration and anti-MCV antibody levels in either psoriasis or PsA groups. But Dalmady et al. demonstrated higher levels of anti-MCV antibodies in patients with early-onset psoriasis. The correlation of nail involvement and anti-MCV antibody positivity was also determined in the PsA group; nevertheless in our study there was no statistically significant correlation between nail involvement and anti-MCV antibody levels [**13**].

Placek et al. investigated the prevalence of anti-MCV in 54 patients with psoriasis with or without joint involvement, by indirect immunoflourescence. The incidence of anti-MCV in patients with plaque psoriasis was found to be similar in patients with also PsA (65.1% vs. 62.5%) [**38**]. Although the prevelance of Anti-MCV in this study was higher than other studies in the literature, this may be due to using immunofluorescence method.

The relationship between smoking and inflammatory diseases and the effect of this relationship on ACPA levels are discussed in some studies. Smoking has been shown to be associated with a reduced response to disease-modifying and biological drugs in RA [**39**]. The relationship between smoking and high levels of ACPAs also supports this effect [**40**]. Nonetheless the mechanism of the smoking-related increase of ACPAs is not known. In our study, correlation of smoking and anti-MCV antibody levels was detected in control group but neither in psoriasis nor in PsA groups.

A study conducted by Tesija-Kuna et al. revealed that median anti-MCV values were significantly higher in patients with PsA compared to healthy controls and other inflammatory rheumatic diseases; but lower than the RA group. At the same time; among patients with PsA, anti-MCV antibodies were found to be statistically significantly higher in patients with asymmetric polyarthritis and dactilitis. This finding was interpreted by the authors as that Anti-MCV might be a marker associated with predominance of polyarticular involvement rather than being spesifical marker of RA [**37**]. Consistent finding was reported by Alenius et al. which show that Anti-CCP, another member of ACPA family, was also correlated with poliarticular involvement [**20,37**]. In our study, no statistically significant correlation was found between type of joint involvement and anti-MCV levels of PsA patients. This may be due to the fact that these subgroups defined according to the type of joint involvement included small number of patients.

It has been suggested that ACPA levels can be used to evaluate the response to treatment in RA [**41**]. Systemic therapies may lead to a decrease in antibody levels; however antibodies rarely become negative [**41,42,43**]. It has been postulated that the severe disease requiring systemic treatment may be associated with high antibody levels, because those receiving systemic therapy in patients with psoriasis have higher anti-MCV antibody values than those who do not receive systemic therapy or phototherapy [**13**]. In our study, no statistically significant relationship was found between the treatment modalities and the anti-MCV antibody levels in both psoriasis and PsA groups. Studies of anti-MCV values

before and after treatment will clarify the effect of treatment on these antibodies.

While ACPAs have been investigated in all aspects of RA, its clinical significance in psoriasis and PsA is unclear. Although the mechanism of the production of autoantibodies are not known, it is suggested that the inflammation caused by the disease may induce the production of autoantibodies by revealing the hidden antigens as a result of cell damage in tissue. In conclusion, although the exact mechanism is unknown, our study suggests that anti-MCV might have a role in the pathogenesis of PsA rather than psoriasis. New studies are needed to demonstrate the pathogenetic and clinical significance of anti-MCV antibody in psoriasis and PsA.

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