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ORIGINAL ARTICLE RHEUMATOLOGY

Anti-mutated citrulline vimentin antibodies may be higher in Ankylosing spondylitis, but may not have a role in diagnosing disease and may not be associated with disease severity

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ABSTRACT

OBJECTIVE: Ankylosing spondylitis (AS) is a rheumatologic disease with severe morbidity and mortality. Many studies in the literature showing that serum antibodies against anti-mutated citrullinated vimentin (anti-MCV ab) can be elevated in rheumatoid arthritis (RA) patients. However, there is little data in the literature about the levels of anti-MCV antibodies in AS patients. We designed the study to evaluate the role of anti-MCV antibody in the diagnosis of AS and to investigate whether it is associated with disease activity parameters.

METHODS: There were three separate groups in our study. The number of participants in these groups is 60 patients in the AS group, 60 patients in the RA group, and 50 healthy participants in the control group. The anti-MCV ab levels of the participants were measured by enzyme-like immune assay method. We compared anti-MCV levels between groups. We then evaluated its role in the diagnosis of AS and evaluated its relationship with disease activity parameters.

RESULTS: The anti-MCV antibody levels of both AS (p=0.006) and RA (p>0.001) patients were found to be significantly higher than controls. Anti-MCV antibody was higher than predefined threshold level (20 IU/mL) in 4 of 60 (6.7%) AS patients. Anti-MCV levels are similar in patients with or without a -acceptable symptom state (PASS). There is also no appropriate anti-MCV cutoff level with respect to PASS and a highly sensitive and specific level for diagnosis of AS.

CONCLUSION: Although AS patients has higher anti-MCV levels than controls, it may have a limited ability to AS diagnosis and to predict severity of the disease.

Keywords: Ankylosing spondylitis; anti-mutated citrullinated vimentin; rheumatoid arthritis.

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Ankylosing spondylitis (AS) is one of the chronic inflammatory rheumatic diseases characterized by inflammatory low back pain, peripheral arthritis, and extra-articular involvements. Etiology of the disease is unknown. The prevalence of AS was found up to be 0.9% in different studies [1]. Rheumatoid arthritis (RA) is one of the most common inflammatory arthritis, and the prevalence of the disease is around 0.5–1% worldwide [2].

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Genetic and environmental factors have a role in the pathogenesis of both diseases. Today, new and more effective treatment approaches such as biological agents have increased the importance of early diagnosis and early treatment. Therefore, new biomarkers are needed for early diagnosis. Anti-citrulline peptide antibodies are specific and sensitive diagnostic markers for RA. However, the efficacy of these autoantibodies in diagnosing AS has yet to be determined [3].

Post-translational modifications of proteins involved in the basic function of cells are common. These modifications make these proteins antigenic targets for autoantibodies. One of the well-known post-translational modifications is citrullination through peptidyl arginine deaminase enzymatic activity [4]. Citrullinated proteins can trigger auto-antibody production in susceptible patients. The best-known examples of these proteins are filagrin, Type 2 collagen, alpha enolase, fibrinogen, and vimentin [5]. In RA patients, autoantibodies to these proteins are sensitive and specific markers for diagnosis. In addition, both citrullinated proteins and autoantibodies to them have contribution to the pathogenesis of RA [6].

Vimentin is an intermediate filament that is abundant in synovial fibroblasts. It is secreted from macrophages that are activated during inflammation by tumor necrosis factor alpha (TNF-α). Their main intracellular functions are to assist the mechanical stability, motility and migration of fibroblasts [7], and increased resistance of endothelial cells to mechanical stress [8]. In addition, vimentin has some functions on the cell surface and extracellular space. It is one of the necessary proteins during the bacterial killing process. In addition, vimentin expressed on the cell surface of neutrophils plays a role in apoptosis. The presence of citrullinated vimentin in synovial fluid has been shown in both RA and spondyloarthropathy [9].

There are little data on the possible role of citrulline proteins in the diagnosis of spondyloarthropathies. In AS, some of the HLA-B27 allelic variants may influence antigen presenting capacities of inflammatory cells. Here, HLA-B*2705 and B*2709 may be associated with increased presentation of citrullinated proteins [10].

Some studies have shown that increased anti-MCV levels in early RA may be more sensitive and specific for diagnostic purpose compared to anti-CCP. In addition, there are two studies in the literature showing that anti-MCV antibodies levels increase in AS patients [3, 11].

Highlight key points

- Anti-MCV does not have a highly sensitive and specific level for the diagnosis of AS.
- Anti-MCV levels are similar in AS patients with or without a patient-acceptable symptom status (PASS).

Although the relationship between vimentin, anti-MCV antibody, and RA is known; there is no study in the literature evaluating the possible benefit of vimentin and anti-MCV antibodies in the diagnosis of AS.

The main aim of the study was to determine its possible utility for the diagnosis of AS by comparing the levels of anti-MCV antibody with those of RA and controls. Next, we evaluated the relationship between disease activity and follow-up parameters and anti-MCV antibody levels in AS patients to predict the severity of the disease.

MATERIALS AND METHODS

We included the participants in three different groups. Two of these groups included patients with RA or AS. The third is the control group who applied to a tertiary center outpatient clinic with mechanical complaints. All participants in the healthy group were evaluated primarily by a rheumatologist to exclude rheumatological diseases. All patients in the RA group met The American Rheumatism Association 1987 Revised Criteria [12] and patients with AS fulfilled modification of the New York criteria [13]. Here, we included 60 patients with RA, 60 patients with AS and finally 50 healthy participants. Healthy participants were matched with the patient groups in terms of mean age of both diseases ±SD.

This study was approved from the Akdeniz University Clinical Research Ethics Committee (date: July 16, 2012 – number: B.30.2.AKD.0.20.05.06/165) and carried out in compliance with the Helsinki Declaration. All the patients gave written informed consent.

Evaluated Clinical Features of Patient Groups

We evaluated age, gender, disease duration, current anti-TNF treatments, bath AS disease activity index (BASDAI), bath AS functional index (BASFI), and bath AS metrology index (BASMI) in the AS group.

BASMI assesses the functional capacity of AS patients with spinal measurements. It consists of 5 different parameters. These parameters are cervical rotation, tragus-wall distance, lateral flexion, modified schober

Table 1. Demographic and disease characteristics of the participants

	RA patients n=60	AS patients n=60	Control n=50	p	*Post-hoc* analyses
Gender (M/F)	9/51+*	49/11+β	19/31β*	<**0.001**	<**0.001**β+ **0.006***
Age (years)	49.3±12.1+*	39.4±10.7+	41.9±13.0*	<**0.001**	<**0.001**+ 0.002*
Disease duration (years)	11.2±9.3	11.4±8.2	N/A	0.62	
Anti-MCV positivity (%)	32 (53.3)+*	4 (6.7)+	1 (2.0)*	<**0.001**	<**0.001**+*
ESR (mm/h)	38.8±23.4	28.8±33.3	N/A	0.10	
CRP (mg/l)	0.8±1.0	1.2±1.3	N/A	0.54	
Anti-MCV levels	172.2±387.3+*	9.9±6.4+β	7.7±4.6β*	<**0.001**	<**0.001**+* 0.006β
DAS 28-ESR	3.6±1.1	N/A	N/A	N/A	
Anti-TNF treatment (%)	41 (68.3)	13 (21.7)	N/A	<**0.001**	

M: Male; F: Female; Anti-MCV: Anti mutated citrullinated vimentin; ESR: Erythrocyte sedimentation rate; CRP: C reactive protein; DAS-28: Disease activity score 28 joints p<0.05 is significant. *Post-hoc* analysis p<0.016 is significant. +: The difference between RA and AS patients in the *post-hoc* analyses; *: The difference between RA patients and controls in the *post-hoc* analyses; □: The difference between AS patients and controls in the *post-hoc* analyses.

and intermalleolar distance measurement, and a maximum of 10 points can be obtained using 0, 1, and 2 points [14]. All measurements were evaluated by the same rheumatologist (NS).

BASDAI is used to measure disease activity in AS patients. BASDAI is a 6-question evaluation test tool that can be easily applied to patients to measure the general condition of the patient for the past week, the feeling of fatigue, the severity of pain in the axial and peripheral joints, swelling and sensitivity of the joints, and the severity and duration of morning stiffness [15].

BASFI assesses the functionality of AS patients. It consists of ten questions asked to determine the functionality of the patients in their daily lives in the last week [16].

Age, gender, duration of diseases, and the current treatments (anti-TNF) of RA patients were evaluated. RF values were recorded from the database of our hospital. Ig M class RF is evaluated in our hospital. Values above 15 U/mL are considered positive. We used the Disease activity score 28-Erythrocyte sedimentation rate (DAS 28-ESR) to assess disease activity.

The number of tender and swollen joints of the patients was determined by the physical examination performed by the same rheumatologist (NS). We then calculated the DAS 28-ESR score using an online calculator [17].

Only the age and genders of the control group were recorded.

PASS was predefined [18]. Patients with both BASDAI ≤4.1 and BASFI ≤3.8 are considered in PASS.

About 5 cc of blood was taken from all cases and their serum was separated. Anti-MCV antibody analysis was studied with ORG 548 anti-MCV kit using ELISA method. (Orgentec Diagnostika, Mainz, Germany). Values over 20 units/mL were considered positive for RA according to the instructions of the manufacturer.

We first compared the anti-MCV ab levels of the three groups. We then evaluated the relationship between antibody levels and disease activity and follow-up parameters in both AS group.

Statistical Analysis

We calculated the sample size of the study with G*Power (Universitat Kiel, Germany). At 75% power, α error level 0.05, and effect size 0.5, the total number of participants needed was 57. All other statistical evaluations were carried out with "Statistical Packages for Social Sciences Version 16.0 for MS Windows" program. The comparisons of the continuous variables between patients were performed by Mann–Whitney U or Kruskal–Wallis test in terms of the number of compared groups. We then conducted post hoc analysis with Bonferonni adjusted Mann–Whitney U or square tests if necessary. More-

TABLE 2. Disease follow up and activity parameters of AS patients

	AS patients n=60
BASDAI	3.4±2.4
BASMI	3.4±2.7
BASFI	2.8±2.3
Uveitis (%)	15 (25.0)
PASS features	
BASDAI ≥4.1 (%)	22 (36.7)
BASFI ≥3.8 (%)	19 (31.7)
BASDAI ≥4.1 or BASFI ≥3.8 (%)	26 (43.3)
BASDAI ≥4.1 and BASFI ≥3.8 (%)	15 (25.0)

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; Basmi: Bath Ankylosing Spondylitis Metrology Index; PASS: Patient-acceptable symptom state; AS: Ankylosing spondylitis.

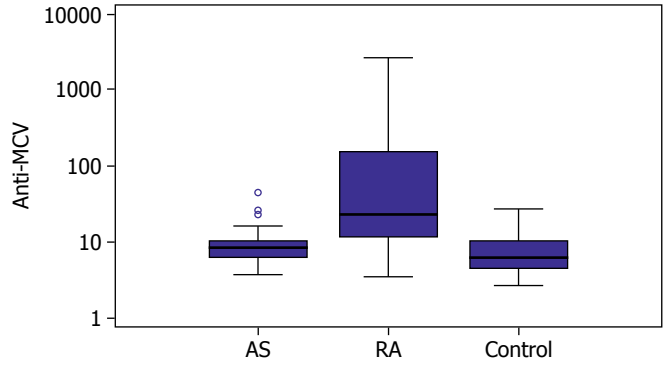

FIGURE 1. Anti-mutated citrullinated vimentin levels of participants.

over, the comparisons of the categorical variables were performed using Chi-square test. We also performed receiver operating characteristic (ROC) analyses to find threshold anti-MCV ab levels related to AS diagnosis and PASS. Area under curve measurements was made to determine the validity of the tests. All values were shown as mean (±SD). P<0.05; considered significant.

RESULTS

Sixty patients with AS (11 women+49 men), 60 patients with RA (51 women+9 men), and 50 participants for the control groups (31 women+19 men) were included in the study.

The mean age of the AS and RA patients was 39.42±10.76 years and 49.33±12.17 years, respectively. In addition, the mean age of the control group was 41.90±13.00 years. RA patients were older then both groups.

Anti-MCV ab levels were significantly higher in the RA group. Antibody levels were higher in both the RA and AS groups than in the control group (Fig. 1). In addition, significantly more patients in the RA group had anti-MCV levels higher than the cutoff levels. However, the frequency of participants with antibody levels higher than the cutoff levels was similar in AS patients and controls.

Demographic and disease-related characteristics of the participants are presented Table 1.

Twenty-six (43.3%) of 60 AS patients were not in PASS. In addition, uveitis was the most frequent extra-articular feature of the AS patients (Table 2). There was no difference between those with and without PASS in terms of anti-MCV levels (p=0.73). Anti-MCV levels in patients with and without PASS were 9.3±4.5 and 10.8±8.39, respectively.

Only four patients in the AS group had anti-MCV levels higher than the RA threshold. All of them were under anti-TNF therapy at the time of the study. In addition, two of the patients were in PASS status.

Although the cutoff level for ant-MCV ab is predefined by the manufacturer as 20 IU/mL, there is no study in the literature defining the anti-MCV ab level cutoff for the diagnosis of AS. Based on ROC analyses, there is no appropriate anti-MCV ab value to diagnose AS with high sensitivity and specificity. The optimal anti-MCV value was 6.8 IU/mL with 75% specificity and 60% sensitivity. The odds ratio for AS with anti-MCV levels >6.8 IU/mL is 1.8 (95% CI 1.2–2.7, p<0.001). In addition, ROC analysis for defining anti-MCV ab levels for patients in PASS state is not significant (p=0.73). Figure 2 shows the ROC analyses for both parameters.

DISCUSSION

In the study evaluating the role of anti-MCV ab in diagnosing AS and predicting its severity, AS patients had higher anti-MCV levels than controls. However, limit levels of anti-MCV for these purposes have not been determined.

AS and RA are inflammatory diseases that negatively affect the quality of life of patients and cause serious morbidity and mortality. Therefore, early diagnosis and treatment are important for both diseases. In RA, RF and anti-CCP positivity together with radiographic findings may help in early diagnosis. However, there are no laboratory markers for early diagnosis of AS.

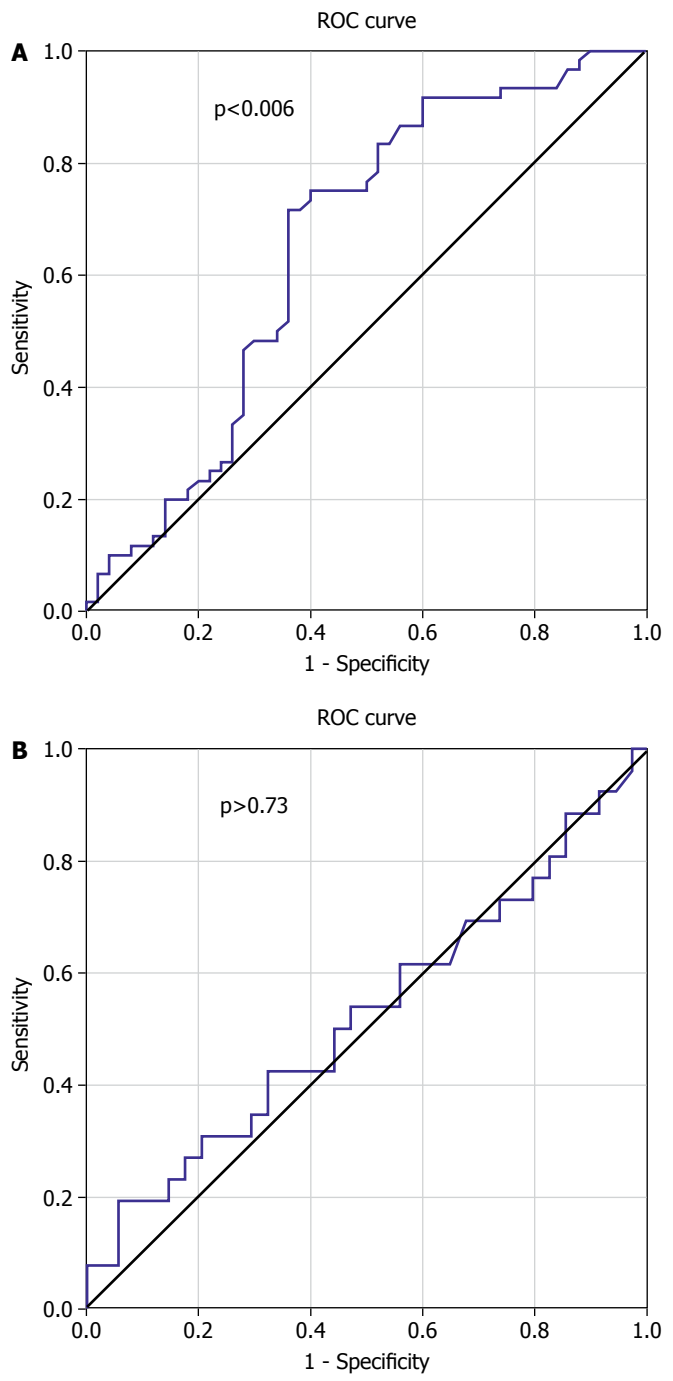

Figure 2. **(A)** Receiver operating characteristic (ROC) figure of anti-mutated citrullinated vimentin (anti-MCV) levels to diagnose Ankylosing spondylitis, **(B)** ROC figure of anti-MCV levels related to patient-acceptable symptom state.

The presence of anti-CCP and anti-MCV antibodies, both of which are anti-citrulline protein antibodies, plays an important role in the early diagnosis of RA. The sensitivity and specificity of anti-MCV have been differentially indicated in various studies. Bang et al. [19] evaluated 1151 RA patients and found anti-MCV antibody sensitivity 82%, specificity 98%, anti-CCP antibody sensitivity 72%, and specificity 96%. In the same study, they found anti-MCV antibodies positive in 43 (22.8%) of 189 systemic lupus erythematosus (SLE) patients, 11 (16.2%) of 68 primary Sjögren's syndrome patients, and 4 (1.7%) of 232 healthy controls. Data published by Poulsom and Charles. showed that the anti-MCV sensitivity was 81% (55/68) in patients with disease duration longer than 2 years, and 92% (22/24) in patients with early RA [20]. In addition, in another study, anti-MCV positivity was found as 14% (7/50) in SLE, 24% (12/50) in Sjögren's Syndrome, and 16% (8/50) in Scleroderma [20]. In our study, 32 (53.3%) of 60 RA patients has anti-MCV ab levels higher than threshold. Positive anti-MCV values were found in only 4 (6.7%) patients in the AS group, while positive anti-MCV values were found in one patient in the controls. However, like the RA group, AS patients had higher absolute anti-MCV levels than controls. Manufacturer defined cutoff value is indicated for RA patients. Therefore, we also tried to define an anti-MCV cut-off value for the diagnosis of AS. Although the diagnostic utility of anti-MCV was statistically confirmed, none of the values matched the high levels of sensitivity or specificity for practical use.

The relationship between anti-MCV levels and disease activity in RA patients has been investigated in studies. Bang et al. [19] found that anti-MCV levels and DAS 28 scores were statistically significant and correlated. In addition, Boire et al. [21] showed that RA patients with positive anti-MCV antibodies had early and more severe joint damage. However, there is no study in the literature showing the role of anti-MCV ab in predicting the course of the disease in AS. The outcome parameter for disease severity in our study was PASS status. We found no difference between patients with and without PASS in terms of anti-MCV ab levels. Interestingly, while two-thirds of all AS patients in our cohort were receiving anti-TNF at the time of the study, all four patients with anti-MCV ab levels >20 IU/mL were using anti-TNF. This may be a sign that patients with higher anti-MCV ab have more severe disease.

HLA-B*2705 and B*2709 variants of HLA-B27 in AS has an increased capacity to present citrullinated proteins [11]. Bodnar et al. [3] investigated anti-MCV levels in 43 AS and 44 healthy controls. Anti-MCV antibodies were found to be positive in 16 (37%) patients with AS (median value 17.3 U/mL, range: 8.3–31.5 U/mL). They did not detect any positive in the control group.

They speculated that anti-MCV positivity could be the new biomarker to diagnose AS. In addition, Siebuhr et al. [22] found a significantly higher rate of positivity of anti-MCV antibodies in both the non-radiographic spondyloarthropathy (10% of 121 patients) and AS (14% of 72 patients) groups compared to healthy controls. However, in our study the positivity rate for anti-MCV ab in AS was lower than this. Here, only 4 (6.7%) of 60 patients with AS were positive for anti-MCV antibody. The low anti-MCV positivity in our cohort may be due to the different penetration frequency of some HLA B27 variants in different populations.

Our study has some limitations. First, the number of patient groups is limited. Then, it was a cross-sectional study without the possibility of prospectively showing the severity of the disease. In addition, due to different nature of AS and RA, the gender frequencies of both diseases were different. Therefore, we did not use gender for matching the groups.

Conclusion

In conclusion, our study aimed to investigate the role of anti-mutated citrullinated vimentin (anti-MCV) antibodies in the diagnosis of ankylosing spondylitis (AS) and their association with disease activity parameters. We compared the levels of anti-MCV antibodies among three groups: AS patients, rheumatoid arthritis (RA) patients, and healthy controls. The findings revealed that both AS and RA patients had significantly higher levels of anti-MCV antibodies compared to the control group. However, the anti-MCV antibody levels in AS patients did not reach a definitive threshold for diagnosis or prediction of disease severity. Although the presence of anti-MCV antibodies may be observed in AS patients, it has limited utility as a diagnostic marker and predictor of disease severity. Further research is needed to explore additional biomarkers and diagnostic criteria for AS.

Ethics Committee Approval: The Akdeniz University Clinical Research Ethics Committee granted approval for this study (date: 16.07.2012, number: B.30.2.AKD.0.20.05.06/165).

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: Concept – NS; Design – SO; Supervision – CK; Materials – GU; Data collection and/or processing – GU; Analysis and/or interpretation – MET; Literature review – NS; Writing – NS; Critical review – MET.

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