Assessment of serum antimutated citrullinated vimentin antibodies in rheumatoid arthritis

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Background
Early diagnosis and treatment of rheumatoid arthritis (RA) leads to better control and prevents irreversible joint damage. Antimutated citrullinated vimentin (anti-MCV) is one of the members of the anticitrullinated antibody family that can function as a serological marker in the early diagnosis of RA.

Aim of the work
This study aimed to measure serum levels of anti-MCV antibodies and study their relationship using clinical, laboratory, and radiological findings in RA patients.

Patients and methods
We measured anti-MCV in the serum of 60 RA patients, in 20 patients with psoriatic arthritis, and in 20 healthy controls. In RA patients, the disease activity score (DAS28) and the Health Assessment Questionnaire score were used. The immunoglobulin-M rheumatoid factor titer, anticyclic citrullinated peptide antibody (anti-CCP) titer, and C-reactive protein levels were also measured. The hands of RA patients were radiologically scored using the Larsen method.

Results
In RA patients the mean anti-MCV antibody serum level was 150.83 ± 125.95 U/ml, which was significantly higher ($P < 0.001$) compared with the mean serum level in psoriatic arthritis patients and healthy controls (17.4 ± 10.039 and 17.2 ± 10.63 U/ml, respectively). Serum levels of anti-MCV antibodies significantly correlated with DAS28 ($r = 0.79$, $P < 0.05$), Health Assessment Questionnaire scores ($r = 0.53$, $P < 0.05$), rheumatoid factor titer ($r = 0.74$, $P < 0.05$), anti-CCP antibody titer ($r = 0.83$, $P < 0.05$), and Larsen's score ($r = 0.76$, $P < 0.05$).

Conclusion
The significantly elevated anti-MCV antibody levels that are well correlated with RA disease activity and severity markers are highly suggestive of their potential role in the pathogenesis of RA. The considerable correlation of anti-MCV antibodies with other autoantibodies would imply their consistent diagnostic and prognostic role.

Keywords:
antimutated citrullinated vimentin, citrullinated proteins, disease activity (DAS28), rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic systemic disease affecting primarily the synovium, leading to joint damage and bone destruction [1]. Early diagnosis of RA and its early treatment with disease-modifying antirheumatic drugs lead to better control and less joint damage. Therefore, it is very important to find an acceptable serological marker in order to make an early diagnosis and initiate early treatment to avoid complications and disability [2].

Various serum biomarkers are used to diagnose RA, including many autoantibodies. However, only rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) antibodies have wide acceptance [3].

Antibodies targeting citrullinated proteins are found to be highly specific for the diagnosis of RA [4]. They have many targets in rheumatoid synovial tissue, including α-fibrin and β-fibrin chains, fibronectin, collagen type I, and α-enolase (from monocytes and granulocytes) in citrullinated form [5–7]. These autoantibodies predict clinical and radiological severity and may be implicated in the pathogenesis of RA; however, they have a high value in the early diagnosis and early treatment of RA [8].

Vimentin is usually not found in citrullinated form *in vivo*, but deamination of arginine residues on vimentin molecules has been demonstrated to occur in macrophages during apoptosis [9]. In a polymerized form, vimentin constitutes a structure of intermediary filaments, the main component of cytoskeleton in

mesenchymal cells (chondrocytes, synovial fibroblasts, and macrophages) [10].

Antimutated citrullinated vimentin (anti-MCV) is another anticitrullinated antibody reacting with MCV [11]. It was discovered through an anti-Sa autoantibody test and was first identified in a French/Canadian patient whose name began with the letters Sa; it was expressed in fibroblasts like synoviocytes [12].

Anti-Sa autoantibodies have the same specificity as anti-CCP antibodies but show too low sensitivity to help in RA diagnosis [13]. Genetic modification of citrullinated vimentin to MCV by enzyme linked immunosorbant assay (ELISA) was developed to increase the sensitivity [14].

This study aimed to measure serum levels of anti-MCV antibodies and study their relationship with clinical, laboratory, and radiological findings in RA patients.

Patients and methods

Study approval
The study was approved by the Ethical Committee of our institution. All patients gave their written informed consent before participation in this study.

Participants
Sixty patients fulfilling the 2010 ACR-EULAR classification criteria for RA [15] were recruited from among the inpatients and outpatients of the Rheumatology and Rehabilitation department of Benha University Hospitals. Twenty age-matched and sex-matched psoriatic arthritis (PsA) patients with inflammatory peripheral arthritis fulfilling the 2006 CASPAR classification criteria for PsA [16] as well as 20 age-matched and sex-matched apparently healthy individuals from among the hospital personnel, undergraduates, and medical and nursing staff were included as controls.

We excluded patients with a known malignancy or chronic infection (e.g. tuberculosis and hepatitis B or C).

Methods
RA patients' evaluation included full history taking with recording of the disease duration, thorough physical examination, with particular focus on the pattern of joint involvement, the presence of nodules and other extra-articular features, and ongoing medications. Disease activity using the 28 joint counts

(DAS28) [17] and Health Assessment Questionnaire (HAQ) score [18] was assessed in all patients. Radiographs (posteroanterior view) of the hands were obtained for all patients and were scored using the Larsen method [19].

Laboratory investigations
About 10 ml of venous blood was collected and analyzed for complete blood count and for evaluation of the erythrocyte sedimentation rate by Westergren's method [20] in mm/h, C-reactive protein (CRP), RF, and anti-CCP antibodies.

Measurement of serum levels of anti-MCV antibodies
Anti-MCV antibody levels were measured in the serum collected from all RA patients, PsA patients, and healthy controls. All blood samples were allowed to clot and the serum was separated by centrifugation and stored at -20°C until analysis. Assay of anti-MCV antibodies was performed by means of the ELISA technique using the human anti-mutated citrullinated vimentin (MCV) antibody ELISA Kit (Cat.No: CSB-E09565h; Cusabio, Hubei, China). The assay procedures were followed as per the manufacturer's instructions. Detection range was from 5 to 400 U/ml, and anti-MCV antibodies were considered positive if the level was greater than 20 U/ml.

Statistical analysis
The collected data were analyzed using SPSS, version 16 (SPSS Inc., Chicago, Illinois, USA). Categorical data were presented as number and percentages, whereas continuous variables were presented as mean and SD if parametric and as median and range if nonparametric. The χ^2-test, the Z-test, the Mann–Whitney U-test, the Kruskal–Wallis test, and Spearman's correlation coefficients were used as tests of significance. A two-sided P-value less than 0.05 was considered significant.

Results
Of the 60 patients with RA, 57 were female (95%) and three were male (5%). Their ages ranged from 20 to 64 years (mean ± SD 41.183 ± 9.18 years). Both control groups were age and sex matched to RA patients; PsA patients' ages ranged from 19 to 63 years (mean ± SD 40.6 ± 12.1 years), whereas the ages of healthy controls ranged from 19 to 63 years (mean ± SD of 43.35 ± 10.5 years). The study groups' clinical and laboratory features are shown in Table 1.

Regarding extra-articular manifestation in RA patients, 14 patients (23.33%) had subcutaneous nodules, eight

patients (13.33%) had interstitial pulmonary fibrosis, and one patient (1.7%) had scleritis.

All patients were receiving NSAIDs, whereas 48 patients (80%) were receiving methotrexate (12.5-20 mg/week) in combination with hydroxychloroquine, eight patients (13.33%) were on leflunomide (20 mg/day) in combination with hydroxychloroquine, and four patients (6.66%) were receiving a combination of methotrexate and leflunomide. Twenty-two patients (36.66%) were on corticosteroids, with a dose ranging from 5 to 20 mg/day.

The mean anti-MCV antibody serum level in RA patients was 150.83 ± 125.95 U/ml, with a highly significant increase ($P < 0.001$) compared with its level in PsA patients and healthy individuals.

No significant difference ($P>0.05$) was found between the mean anti-MCV antibody serum level in PsA patients (17.4 ± 10.039 U/ml) and the level in healthy individuals (17.2 ± 10.63 U/ml).

Regarding the distribution of autoantibodies in RA patients, both anti-CCP and anti-MCV antibodies were positive in 39 patients (65%) and negative in 10 patients (16.67%). Positive anti-MCV and negative anti-CCP antibodies were found in seven patients (11.67%), whereas negative anti-MCV and positive anti-CCP antibodies were found in four patients (6.67%) (Table 2).

Forty-six RA patients (76.6%) were positive for anti-MCV antibodies, with a highly significant increase ($P < 0.001$) compared with PsA patients (1/20, 5%) and healthy control groups (1/20, 5%).

The receiver operating characteristic curve for anti-MCV antibodies was drawn (Fig. 1); the area under the curve was 0.881 at 95% confidence interval. Sensitivity was 76.6% and specificity was 95% in diagnosing RA patients, with a positive predictive value (PPV) of 95.83, a negative predictive value (NPV) of 74.07, and accuracy of 84%.

Sensitivity of anti-CCP antibodies was 71.67% and specificity was 95% in diagnosing RA patients with a PPV of 95.56, NPV of 69.09, and accuracy of 81%. The RF had a sensitivity of 83.33% and specificity of 85% in diagnosing RA patients with a PPV of 89.29, NPV of 77.27, and accuracy of 84%.

The mean anti-MCV antibody serum level in RF-positive RA patients ($n = 50$) (162.34 ± 128.33 U/ml) showed a highly statistically significant increase ($P < 0.001$) compared with RF-negative patients ($n = 10$) (86.3 ± 72.03 U/ml).

Table 1 Clinical and laboratory characteristics, disease activity, radiological severity, and functional disability of the rheumatoid arthritis patients

| Characteristics	Mean ± SD	Range
Disease duration (years)	6.78 ± 4.21	2–121–12
Tender joints (N)	11.67 ± 2.4	2–23
Swollen joints (N)	7.2 ± 2.25	0–15
Morning stiffness (min)	83.00 ± 33.98	30–150
ESR (mm/first hour)	61.58 ± 18.64	20–120
CRP (mg/dl)	37.03 ± 15.98	6–96
HB (g/dl)	10.98 ± 1.7	7–13
WBCs/mm³	7.7 ± 2.1	4.000–12.000
Rheumatoid factor (U/ml)	26.91 ± 10.17	4–120
Anti-CCP (U/ml)	93.95 ± 75.97	16–300
Anti-MCV (U/ml)	150.83 ± 125.95	5–400
DAS28	4.6 ± 0.78	1.8–8
Larsen score	58.8 ± 13.5	40–85
HAQ	1.12 ± 0.71	0.4–2.7

Anti-CCP, anticyclic citrullinated peptide; anti-MCV, antimutated citrullinated vimentin; CRP, C-reactive protein; DAS, disease activity score; ESR, erythrocyte sedimentation rate; HAQ, Health assessment questionnaire; HB, hemoglobin; WBCs, white blood cells.

Table 2 Distribution of rheumatoid arthritis patients according to the presence of RF, anti-CCP, and anti-MCV antibodies

	Anti-CCP positive ($n = 43$)	Anti-CCP negative ($n = 17$)
Anti-MCV		
Positive	39	7
Negative	4	10
Rheumatoid factor positive ($n = 50$)		
Anti-MCV positive	33	5
Anti-MCV negative	3	9
Rheumatoid factor negative ($n = 10$)		
Anti-MCV positive	6	2
Anti-MCV negative	1	1

Anti-CCP, anticyclic citrullinated peptide; anti-MCV, antimutated citrullinated vimentin; RF, rheumatoid factor.

Figure 1
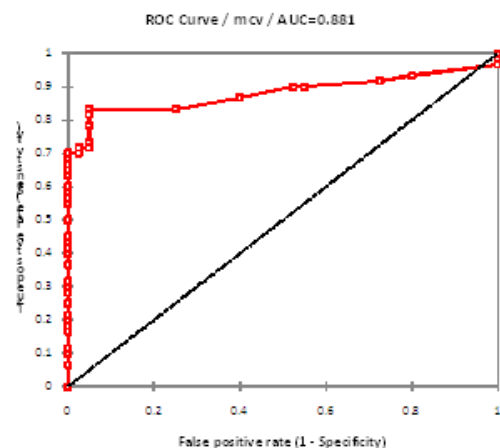
ROC curve assessing the validity of the anti-MCV test in diagnosing RA. The area under the curve was 0.881 at 95% CI. AUC, area under the curve; CI, confidence interval; MCV, mutated citrullinated vimentin; RA, rheumatoid arthritis; ROC, receiver operating characteristic.

Anti-MCV antibody serum levels in RA patients showed a statistically significant correlation with CRP level ($r = 0.47$, $P < 0.05$), DAS28 ($r = 0.788$, $P < 0.05$), HAQ scores ($r = 0.53$, $P < 0.05$), RF titer ($r = 0.74$, $P < 0.05$), anti-CCP titer ($r = 0.83$, $P < 0.05$), and Larsen score ($r = 0.76$, $P < 0.05$) (Table 3).

RA patients with positive anti-MCV antibodies showed a statistically significant increase in swollen joints count ($P < 0.05$), DAS28 ($P < 0.05$), anti-CCP antibody titer ($P < 0.05$), and Larsen score ($P < 0.05$), compared with RA patients with negative anti-MCV antibodies (Table 4).

The linear regression curve showed a significant correlation between DAS and anti-MCV antibody serum levels ($r = 0.788$, $P < 0.05$) (Fig. 2) and between DAS and anti-CCP antibodies ($r = 0.565$, $P < 0.05$), but no significant correlation existed between DAS and RF titer ($r = 0.265$, $P > 0.05$).

Discussion

RA is an autoimmune inflammatory disease characterized by the presence of several autoantibodies. The best known is the RF, which is an autoantibody listed among the diagnostic criteria. The value of RF in the diagnosis, assessment, and evaluation of RA may be controversial [21]. Anti-MCV antibody is a member of the family of autoantibodies reactive with citrullinated proteins that seem to be highly specific for RA. They have a possible prognostic value as a marker of a more serious disease [22].

In our study, serum levels of anti-MCV antibodies were significantly elevated in RA patients than in PsA

Figure 2

Correlations between levels of anti-MCV antibodies and disease activity score (DAS) in rheumatoid arthritis (RA) patients. MCV, mutated citrullinated vimentin.

patients and healthy controls ($P < 0.001$ and $P < 0.001$, respectively) and they have a sensitivity of 76.6% and specificity of 95% in diagnosing RA. Our results confirmed the results of other studies that found an elevated serum anti-MCV antibody level in RA patients than in controls [11,12,23,24].

Tesija-Kuna *et al.* [25] found anti-MCV antibodies in only two out of 56 (3.6%) PsA patients with polyarthritic disease and claimed that anti-MCV antibodies are primarily related to the polyarthritic pattern rather than to the specific diagnosis of RA

Table 3 Correlations between anti-MCV antibody serum levels and different variables in rheumatoid arthritis patients

| Variable in RA patients	Anti-MCV	
	Correlation coefficient (*r*)	*P*-value
Age (years)	0.09	>0.05
Disease duration (years)	0.13	>0.05
Tender joint count	0.62	<0.05*
Swollen joint count	0.71	<0.05*
ESR (mm/first hour)	0.28	>0.05
C-reactive protein (mg/dl)	0.47	<0.05*
DAS28	0.79	<0.05*
Rheumatoid factor	0.74	<0.05*
Anti-CCP antibodies	0.83	<0.05*
HAQ score	0.53	<0.05*
Larsen score	0.76	<0.05*

Anti-MCV, antimutated citrullinated vimentin; CCP, cyclic citrullinated peptide; DAS, disease activity score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; *Significant $P < 0.05$.

Table 4 Comparisons of clinical and laboratory characteristics of rheumatoid arthritis patients according to anti-MCV positivity

Variable in RA	Mean ± SD		*P*-value
	Anti-MCV positive (*n* = 46)	Anti-MCV negative (*n* = 14)	
Age (years)	42.65 ± 13.23	36.29 ± 12.83	>0.05
Disease duration (years)	6.13 ± 5.24	4.65 ± 2.91	>0.05
Tender joint count	12.22 ± 5.52	8.43 ± 4.28	>0.05
Swollen joint count	7.91 ± 3.58	4.86 ± 3.24	<0.05*
ESR (mm/first hour)	63.26 ± 29.41	55.71 ± 22.44	>0.05
C-reactive protein (mg/dl)	38.91 ± 37.27	31.29 ± 27.85	>0.05
DAS28	4.91 ± 1.71	2.39 ± 1.07	<0.05*
Rheumatoid factor (U/ml)	33.11 ± 28.76	30.43 ± 26.91	>0.05
Anti-CCP (U/ml)	108.63 ± 75.81	52.86 ± 43.8	<0.05*
Larsen score	64.74 ± 38.01	41.29 ± 35.88	<0.05*
HAQ	1.18 ± 0.76	0.95 ± 0.55	>0.05

Anti-MCV, antimutated citrullinated vimentin; CCP, cyclic citrullinated peptide; DAS, disease activity score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; *Significant $P < 0.05$.
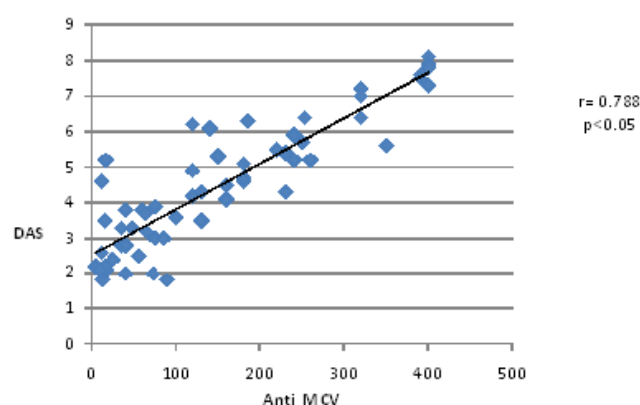
as a concomitant disease. This was comparable to our finding of anti-MCV antibodies in 1/20 (5%) PsA patients.

We found anti-MCV antibody serum levels to be significantly correlated with the clinical and laboratory parameters of RA disease activity, DAS28, and HAQ scores. Our results were in agreement with the results of Keskin *et al.* [26], who found that anti-MCV antibody levels were strongly correlated with disease activity parameters in 427 RA patients, including DAS28, erythrocyte sedimentation rate, CRP, and tender joint count. In a 3-year follow-up study of these patients, the anti-CCP antibody titer failed to show this correlation.

Mathsson *et al.* [12] suggested that anti-MCV antibodies are better predictors of RA disease activity compared with anti-CCP.

In contrast, Ursum *et al.* [27] found low correlation between anti-MCV antibodies and disease activity in early RA patients.

We found anti-MCV antibodies to be positive in 11.7% of RA patients who were negative for anti-CCP. Ronald *et al.* [28] tested both anti-MCV and anti-CCP in 156 patients and found anti-MCV antibodies to be positive in 5.8% of RA patients who were negative for anti-CCP and suggested that the anti-MCV-positive/anti-CCP-negative profile may have a specific gene polymorphism as in the RF, which is associated with a mutation in the protein tyrosine phosphatase nonreceptor type 22 (PTPN22) [29], and anti-CCP, which is associated with polymorphism in PTPN22 1858 C/T [30].

The significant correlations between anti-MCV antibodies and Larsen score in our RA patients were in agreement with many studies. Innala *et al.* [31] reported that anti-MCV-positive RA patients already had significantly greater radiological damage scores compared with anti-MCV-negative RA patients, whereas Syversen *et al.* [32] reported that anti-MCV antibodies were strong predictors of radiological progression in RA patients.

Conclusion

The significantly elevated anti-MCV antibody levels that are well correlated with RA disease activity and severity markers are highly suggestive of their potential role in the pathogenesis of RA. The considerable correlation of anti-MCV antibodies with other autoantibodies would imply their consistent diagnostic and prognostic role.

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