

The Role of Anti-Mutated Citrullinated Vimentin Antibodies in the Diagnosis of Early Rheumatoid Arthritis

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ABSTRACT. *Objective.* Anti-mutated citrullinated vimentin (MCV) antibodies have been reported as a fairly sensitive serological marker of rheumatoid arthritis (RA). We evaluated the diagnostic value of anti-MCV in a large cohort of Chinese patients with early RA.

Methods. One hundred seventy patients with early RA (< 1 yr duration), 66 with other rheumatic diseases, 10 with infectious diseases, and 60 healthy individuals were included in our study. Serum anti-MCV and second-generation anti-cyclic citrullinated peptide antibodies (anti-CCP2) were measured by ELISA, and rheumatoid factor (RF) was measured by rate nephelometry. The associated clinical data of patients with early RA were also evaluated. Then disease activity was scored by the formula for Disease Activity Score (DAS)28, and the degree of radiological changes was assessed by Sharp score.

Results. The prevalence of serum anti-MCV in patients with early RA (78.2%, 133/170) was significantly higher than that of other rheumatologic patients and patients with infectious diseases. It was 12% (3/25) in systemic lupus erythematosus, 9.5% (2/21) in primary Sjögren's syndrome, 10% (1/10) in systemic sclerosis, 20% (2/10) in ankylosing spondylitis, 12.5% (1/8) in viral hepatitis type B, and 0% (0/2) in tuberculosis. Anti-MCV was not found in the serum of healthy subjects. The sensitivities of anti-MCV, anti-CCP2, and RF tests for early RA were 78.2%, 61.8%, and 72.4%, respectively, and the specificities were 93.4%, 96.3%, and 80.1%. The combination of anti-MCV and anti-CCP2 positivity showed a very high specificity (97.8%) and positive predictive value (97.1%), but a low sensitivity (58.8%). The sensitivity reached 81.2% when the union of anti-MCV and anti-CCP2 positivities was used as one combined criterion. Statistically, anti-MCV had significant correlation with anti-CCP2 ($r = 0.587$, $p = 0.01$, 2-tailed) and RF ($r = 0.389$, $p = 0.01$, 2-tailed). In addition, it had an interesting correlation with radiological assessment ($r = 0.349$, $p = 0.05$, 2-tailed). The anti-MCV had no significant correlation with other factors, such as erythrocyte sedimentation rate, C-reactive protein, antikeratin antibody, antiperinuclear factor, global visual analog scale score for joint pain, IgA, IgG, IgM, C3, C4, hidden rheumatoid factor for IgA (HRFIgA), HRFIgG, and DAS28.

Conclusion. Anti-MCV is a novel diagnostic marker for early RA. It may be more useful if the anti-CCP2 assay is performed concomitantly to diagnose patients with early RA. (First Release May 15 2009; J Rheumatol 2009;36:1136–42; doi:10.3899/jrheum.080796)

Key Indexing Terms:

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DIAGNOSIS

Rheumatoid arthritis (RA) is the most common inflammatory joint disease, affecting 0.5%–1% of the world population¹. Chronic inflammation of the affected joints leads to progressive loss of function, which, together with the development of extraarticular manifestations and possible

adverse events of therapy, may increase morbidity and mortality of patients with RA^{2,3}. Increasing evidence shows that therapeutic intervention early in the course of RA results in more efficient disease control, less joint damage, and better prognosis of disease outcome^{2–5}. Thus, rheumatologists are making efforts to find better diagnostic and prognostic markers of early RA.

Rheumatoid factor (RF), the first autoantibody correlated with RA, is directed at the Fc region of IgG and is usually in IgM isotype⁶. It is the commonly accepted and widely used serologic test for RA; however, it is not specific in diagnosing early RA⁷.

Anti-citrullinated protein antibodies (ACPA) have been reported as more specific serological markers of RA. They provide a superior alternative to the RF test in laboratory

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diagnostics of RA⁸⁻¹⁰. This autoantibody family is an overlapping group of antibodies dependent on the citrullination of arginine residue. It includes antiperinuclear factor (APF)^{11,12}, antikeratin antibody (AKA)¹³, antifilaggrin antibodies (AFA)¹⁴, anti-Sa¹⁵, and anti-cyclic citrullinated peptide (CCP) antibodies^{16,17}. Nevertheless, only anti-CCP antibody is used in clinical practice.

Several citrullinated proteins have been demonstrated in the synovium of patients with RA. The identification of citrullinated epitopes as targets for AFA led to the development of the first and second-generation anti-CCP (CCP1 and CCP2) antibody assays. The widely used anti-CCP2 assay has high diagnostic specificity, and it also shows important predictive and prognostic value in RA^{18,19}.

Citrullinated vimentin, identified as the antigenic target for anti-Sa²⁰, is a new member of the family of ACPA. Vimentin is secreted and citrullinated by macrophages depending on the proinflammatory signals^{21,22}. To detect IgG antibodies against citrullinated vimentin, an ELISA system was recently developed²³. Because the assay utilizes mutated citrullinated vimentin (MCV), the performance of the test was improved. Then, some studies showed that it is more sensitive comparing to other antibodies against citrulline-containing epitopes for RA diagnosis²³⁻²⁶. Other studies showed that anti-MCV was presented even earlier in the course of RA than CCP, and therefore was a better marker of early RA²⁷.

We evaluated the diagnostic value of anti-MCV antibodies by ELISA in patients with early RA. Ours is the first study performed in a large cohort of Chinese patients. Moreover, the disease duration of these patients with RA was less than 1 year.

MATERIALS AND METHODS

Patients and serum samples. Serum samples were obtained from 170 patients with RA, 66 with other rheumatic diseases, and 10 with infectious diseases, who were admitted to the Department of Rheumatology and Immunology of Peking University People's Hospital from January 2004 to May 2008. Sixty serum samples from blood donors were used as healthy controls.

The duration of disease in the 170 patients with RA (119 women, 51 men; median age 53 yrs, range 16–83) was less than 1 year, and the median disease duration was 6 months (range 1–12 mo). The diagnosis of these patients fulfilled the American College of Rheumatology (ACR) criteria for RA²⁸.

The 66 patients with other rheumatic diseases and 10 with infectious diseases served as disease controls. They included 25 patients with systemic lupus erythematosus (SLE; 23 women, 2 men; median age 36 yrs, range 28–73), 21 with primary Sjögren's syndrome (pSS; 21 women; median age 58, range 35–79), 10 with systemic sclerosis (SSc; 9 women, 1 man; median age 50, range 30–79), 10 with ankylosing spondylitis (AS; 1 woman, 9 men; median age 33, range 25–38), 8 with viral hepatitis type B (1 woman, 7 men; median age 46, range 38–80), and 2 with tuberculosis (TB; 1 woman, 1 man; median age 38, range 25–52). These 76 patients fulfilled the respective classification criteria^{29,30}.

Serum samples were collected from the patients on medical visits to our hospital, and were split into aliquots and stored at –80°C until assayed.

The protocol used in our study was approved by the Ethical Committee of Peking University People's Hospital (FWA00001384).

Antibody measurements. Anti-MCV antibodies were performed using a commercial ELISA kit (Orgentec Diagnostica GmbH, Mainz, Germany). The best cutoff point was determined by receiver-operating curves (ROC). Meanwhile, the second-generation anti-CCP2 antibody reactivity was tested using the second-generation ELISA kit (Fuchun-Zhongnan Biotech Co., Shanghai, China) with a cutoff value of 25 U/ml. RF (IgM) in serum was measured by the rate nephelometry (Immager; Beckman Coulter, Fullerton, CA, USA); values above 20 U/ml for RF were considered positive.

Clinical and laboratory measures. When the serum samples were collected, the following clinical and laboratory data were collected: age, sex, disease duration, number of swollen joints, number of tender joints, global visual analog scale (VAS) score, immunoglobulins (IgG, IgM, IgA), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement (C3, C4), AKA, APF, and hidden rheumatoid factor (HRFIgA, HRFIgG). Regarding the laboratory features, ESR was measured by the Westergren method; values < 15 mm/h for men and < 20 mm/h for women were considered normal. CRP, immunoglobulins, and complement were examined by immunonephelometry method. The values above 7.9 mg/l for CRP were considered positive. The normal ranges of IgG, IgM, IgA, C3, and C4 were 6.94–16.18 g/l, 0.60–2.63 g/l, 0.68–3.78 g/l, 0.88–2.01 g/l, and 0.16–0.47 g/l, respectively. AKA and APF were tested by indirect immunofluorescence assay. HRFIgA and HRFIgG are immunoglobulin classes of RF. They were tested by ELISA after separation and dissociation of immune complex (IC) with normal ranges of 0–120 U/ml and 0–110 U/ml.

Radiographs of the hands of patients with RA were studied by 2 experienced radiologists blinded to patients' clinical and laboratory data. Radiographs were scored according to the Sharp-van der Heijde method³¹. The Disease Activity Score (DAS28) was calculated as described by van Riel³².

Statistical analysis. Data analyses were performed using SPSS for Windows, version 13.0. For normally distributed data, the results were expressed as mean ± standard deviation (SD); differences between groups were analyzed with the t test. Data not distributed normally were expressed as median (range). The differences were tested with the Mann-Whitney U-test, and correlations were determined by computing Spearman rank correlation coefficients. The diagnostic performance of antibody assays was examined by ROC analysis, by plotting sensitivity against 1 – specificity at different cutoff values. P values less than 0.05 were considered statistically significant.

RESULTS

Sensitivity and specificity of anti-MCV, anti-CCP2, and RF (IgM). Patients with early RA tested positive for anti-MCV at a very high rate [78.2% (133/170)]. Only 6.6% (9/136) of controls showed anti-MCV positive reaction, including 3 patients with SLE patients, 2 with pSS, 1 with SSc, 2 with AS, 1 with viral hepatitis type B, and no healthy individuals. The sensitivity was 78.2% and specificity was 93.4% (Tables 1 and 2). The mean titer of serum anti-MCV in patients with early RA (523.9 ± 660.45 U/ml) was significantly higher than in other patients: only 23.0 ± 12.7 U/ml in SLE, 19.53 ± 14.25 U/ml in pSS, 20.33 ± 5.42 U/ml in SSc, 25.73 ± 17.61 U/ml in AS, 25.36 ± 7.04 U/ml in viral hepatitis type B, and 15.1 ± 0.42 U/ml in TB (Figure 1).

The anti-CCP2 was positive in 61.8% (105/170) of the early RA cases, and in 3.7% (5/136) of controls. The sensitivity was 61.8%, specificity 96.3%, positive predictive value (PPV) 95.5%, and negative predictive value (NPV) 66.8% (Tables 1 and 2).

Further, the prevalence of RF (IgM) was positive in

Table 1. Diagnostic properties of anti-MCV, anti-CCP2, and RF assays using optimal cutoff values.

Assay	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC	95% CI	p
Anti-MCV	78.2	93.4	93.7	77.4	0.93	0.89–0.95	< 0.05
Anti-CCP2	61.8	96.3	95.5	66.8	0.85	0.80–0.89	< 0.05
RF	72.4	80.1	82.0	69.9	0.74	0.68–0.80	< 0.05

CI: confidence interval; MCV: mutated citrullinated vimentin; CCP: cyclic citrullinated peptide; RF: rheumatoid factor; PPV/NPV: positive/negative predictive value; AUC: area under the curve.

Table 2. Prevalence of anti-MCV, anti-CCP2, and RF in patients with different rheumatic diseases, infectious diseases, and healthy individuals.

Group	N	No. Anti-MCV-positive Patients (%)	No. Anti-CCP2-positive Patients (%)	No. RF-positive Patients (%)
Early RA	170	133 (78.2*)	105 (61.8)	123 (72.4)
SLE	25	3 (12)	2 (8)	5 (28)
pSS	21	2 (9.5)	2 (9.5)	6 (28.6)
SSc	10	1 (10)	1 (10)	3 (30)
AS	10	2 (20)	0 (0)	2 (20)
Viral hepatitis type B	8	1 (12.5)	0 (0)	1 (12.5)
TB	2	0 (0)	0 (0)	0 (0)
Healthy individuals	60	0 (0)	0 (0)	10 (16.7)

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; pSS: primary Sjögren's syndrome; AS: ankylosing spondylitis. SSc: systemic sclerosis.

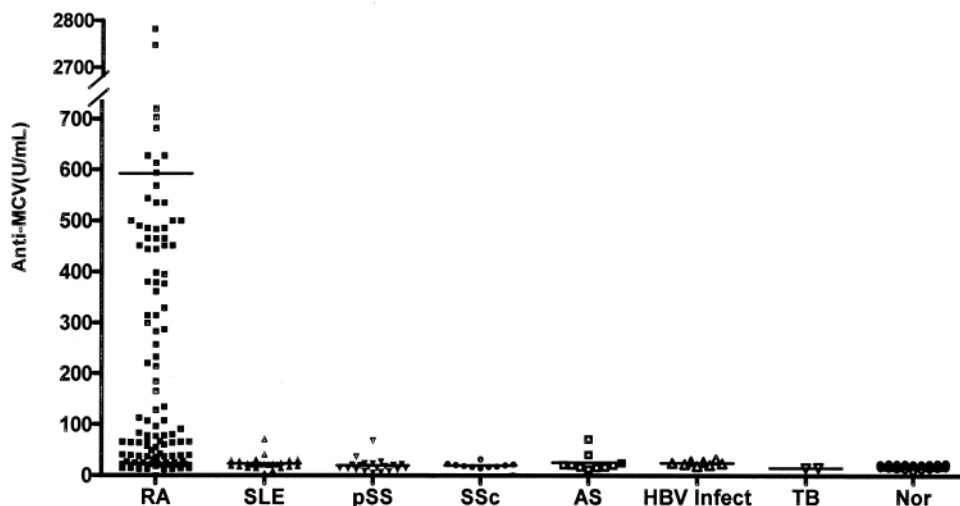


Figure 1. Distribution of anti-MCV antibodies in early RA, other rheumatic diseases, infectious diseases, and healthy individuals. Sera were from 170 patients with early RA, 25 with SLE, 21 with pSS, 10 with SSc, 10 with AS, 8 with HBV, 2 with TB, and 60 healthy individuals (Nor). Titer is expressed as arbitrary units.

72.4% (123/170) of the early RA cases and in 19.9% (27/136) of the controls. The sensitivity was 72.4%, specificity 80.1%, PPV 82.0%, and NPV 69.9% (Tables 1 and 2).

The area under the ROC curve (AUC) with the anti-MCV test [0.93; 95% confidence interval (CI) 0.89–0.95] was higher than that obtained with the anti-CCP2 test (0.85; 95% CI 0.80–0.89) and the RF test (0.74; 95% CI 0.68–0.80) ($p < 0.05$; Figure 2).

Combination of anti-MCV, anti-CCP2, and RF (IgM). In our study, the combination of anti-MCV and anti-CCP2 positivity had the highest specificity (97.8%) and PPV (97.1%), but it had a rather low sensitivity (58.8%). When either anti-MCV or anti-CCP2 positivity was considered as 1 criterion, we got the highest sensitivity value (81.2%). However, the specificity decreased to 92.0% (Table 3). Taking all factors together suggests that the combination of

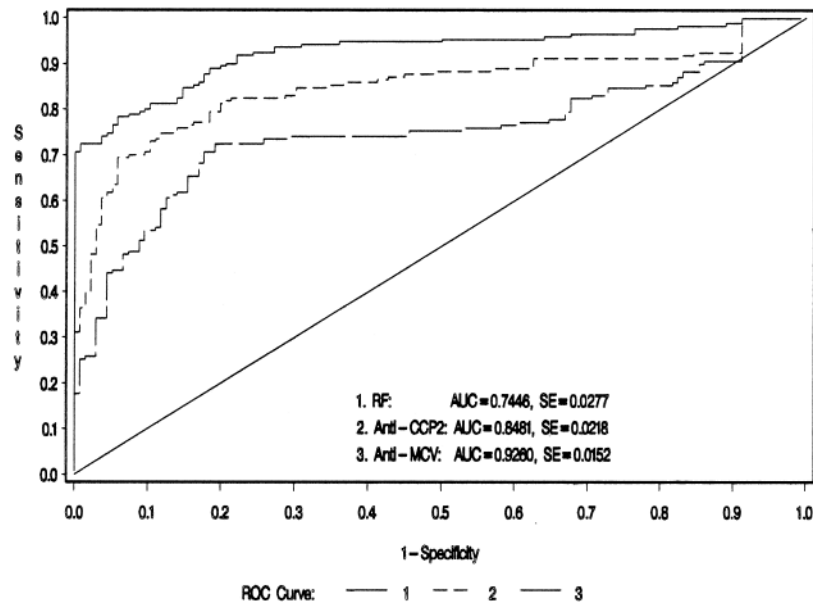


Figure 2. ROC curves of anti-MCV, anti-CCP2, and RF based on data obtained from patients with early RA (n = 170) and controls (n = 136).

Table 3. Diagnostic sensitivity and specificity of anti-MCV, anti-CCP2, and RF combination assays using optimal cutoff values.

	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Anti-MCV and anti-CCP2	58.8	97.8	97.1	65.5
Anti-MCV or anti-CCP2	81.2	92.0	92.6	79.6
Anti-MCV and RF	70.6	96.3	96.0	72.4
Anti-MCV or RF	80.0	77.2	81.4	75.5
Anti-CCP2 and RF	58.8	97.1	96.2	65.3
Anti-CCP2 or RF	75.3	79.4	82.1	72.0

For abbreviations, see Table 1.

anti-MCV and anti-CCP2 is the most effective method in the diagnosis of early RA.

Associations between anti-MCV and clinical features in RA. Demographic, clinical, and serologic characteristics of the patients with early RA are described according to the presence or absence of anti-MCV antibodies in Table 4. Among the 170 patients with early RA, there were no significant differences between the 37 patients who were anti-MCV-negative and the 133 who were anti-MCV-positive with respect to age, sex, disease duration, and most clinical features. But the mean titer of anti-CCP2 antibodies and RF was significantly higher in the anti-MCV-positive group compared to the negative group (anti-CCP2, 411.46 ± 465.69 U/ml vs 87.23 ± 269.80 U/ml; $p < 0.001$; and RF, 119 U/ml vs 38.65 U/ml; $p < 0.05$). With regard to radiographic progression, the Sharp scores of the anti-MCV-positive patients were significantly higher than the negative group.

Anti-MCV had significant correlation with anti-CCP2 ($r = 0.587$, $p = 0.01$, 2-tailed) and RF ($r = 0.389$, $p = 0.01$,

2-tailed). It also had an inferior but important correlation with radiological assessment results ($r = 0.349$, $p = 0.05$, 2-tailed). However, it showed no significant statistical correlation with other factors such as ESR, CRP, AKA, APF, global VAS, IgA, IgG, IgM, C3, C4, HRFIgA, HRFIgG and DAS28.

DISCUSSION

Numerous serological markers of RA have been described over the past 50 years^{6,11-20}. Among all these, ACPA have been proven to be specific diagnostic and prognostic markers in RA. The newest member of this autoantibody family is anti-MCV. The objective of our study was to assess the value of the anti-MCV assay, and to compare it to the diagnostic performance of the commonly used anti-CCP2 and RF tests.

In the detection of serum anti-MCV, the reference normal and pathological ranges are provided in ELISA kits, which should only be regarded as guidelines. Considering there are

Table 4. Clinical and laboratory features of early RA patients with anti-MCV.

	Early RA Anti-MCV-positive, n = 133	Early RA Anti-MCV-negative, n = 37	T	p
Age, median, yrs	54 (22–82)	53 (16–83)		
Sex, no. (%) female	91 (68.42)	28 (75.68)		
Disease duration, median mo	6 (1–12)	6 (1–12)	0.068	0.946
No. tender joints, median	4 (0–28)	4 (0–18)	0.151	0.881
No. swollen joints, median	3 (0–24)	3 (0–18)	0.256	0.798
ESR, mean \pm SD, mm/h	60.54 \pm 33.53	56.89 \pm 37.37	0.571	0.569
DAS28, mean \pm SD	4.81 \pm 1.09	4.71 \pm 0.98	0.544	0.587
CRP level, median mg/l	25.8 (0.11–1296.0)	10.2 (1.26–139.0)	1.126	0.260
Global VAS score, mean \pm SD	41.02 \pm 9.61	38.65 \pm 8.22	1.365	0.174
RF, U/ml	119 (0–4531)	38.64 (0–1450)	5.257	0.040 [†]
IgA, median g/l	3.02 (0–80)	2.53 (0.17–12.6)	0.851	0.396
IgG, median g/l	14.6 (0–560)	12.40 (0–23.4)	1.438	0.152
IgM, median g/l	1.23 (0–15.8)	1.03 (0–13.4)	0.017	0.987
C3, mean \pm SD, g/l	1.08 \pm 0.40	1.11 \pm 0.47	0.392	0.695
C4, mean \pm SD, g/l	0.26 \pm 0.16	0.28 \pm 0.22	0.592	0.555
AKA, median	0 (0–40)	0 (0–10)	1.369	0.173
APF, median	0 (0–10)	0 (0–10)	0.538	0.592
HRFIgA, median U/ml	0 (0–770)	0 (0–1100)	0.287	0.774
HRFIgG, median U/ml	0 (0–1920)	0 (0–1249)	1.250	0.213
CCP2, mean \pm SD, U/ml	411.46 \pm 465.69	89.75 \pm 269.80	5.405	0.000 ^{††}
MCV, mean \pm SD, U/ml	663.6 \pm 684.21	21.85 \pm 5.15	10.82	0.000*
Radiographic progression, median				
Joint-space narrowing score	22 (2–68)	6 (0–80)		0.003**
Erosion score	5 (0–110)	1 (0–27)		0.001***

For normally distributed data, results were expressed as mean \pm SD; differences between groups were analyzed with the t test. Data not distributed normally expressed as median (range), differences were tested with the Mann-Whitney U-test, and correlations were determined by computing Spearman rank correlation coefficients. P values less than 0.05 were considered statistically significant. [†] $p < 0.05$ versus anti-MCV-positive patients. ^{††} $p < 0.001$ versus anti-MCV-positive patients. * $p < 0.001$ versus anti-MCV-positive patients. ** $p < 0.01$ versus anti-MCV-positive patients. *** $p < 0.001$ versus anti-MCV-positive patients. RA: rheumatoid arthritis; MCV: mutated citrullinated vimentin; ESR: erythrocyte sedimentation rate; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; VAS: visual analog scale; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; SD: standard deviation. AKA: antikeratin antibody; APF: antiperinuclear factor; HRF: hidden rheumatoid factor.

no worldwide acceptable serum anti-MCV cutoff values, and there have been few reports in Chinese populations, it is necessary to set a reasonable cutoff value. Our study showed the anti-MCV of 60 healthy individuals ranged from 9.5 U/ml to 25.5 U/ml, where the median titer was 20.6 U/ml. Correspondingly, the specificity at the cutoff value of 20 U/ml was only 45.6%. Then we compared 30 U/ml and 40 U/ml and found that the former had advantages on sensitivity and NPV, while the latter was slightly better on specificity and PPV. Moreover, the best Youden's index was obtained at the cutoff value of 30 U/ml. Taking all factors into consideration, the cutoff value of 30 U/ml was chosen in our study (Table 5).

Comparing patients with early RA with controls, the anti-MCV antibody has been reported to have a sensitivity of 65%–82%, specificity of 80%–97%, PPV 90%, and NPV 78.8%^{23–27}. Moreover, several different types of statistical analysis showed that anti-MCV is more powerful for diagnosing early RA than anti-CCP2. Our findings, which indi-

cated that anti-MCV antibodies were more sensitive for early RA, agree with other studies. In our cohort, the global prevalence of anti-MCV antibodies was 78.2%, which is higher than the prevalence of anti-CCP2 and RF. The specificity of anti-MCV (93.4%) was also much higher than RF but a little lower than anti-CCP2. We suppose that it is because vimentin contains 43 arginine residues, which can potentially be citrullinated. In contrast, in the anti-CCP2 test only a few epitopes are present^{33,34}. The structure of MCV provides optimal exposure of the citrulline residues, enhancing recognition of the protein by the autoantibodies and therefore increasing the sensitivity of the assay.

Our study was designed to evaluate not only the clinical utility of anti-MCV in early RA, but also the physical effect of every possible binary combination, both intersection and union, among anti-MCV, RF, and anti-CCP2. Out of all evaluated combinations, it showed that the most clinically useful test was the union of anti-MCV-positive and anti-CCP2-positive that can produce not only the highest sensitivity

Table 5. Sensitivity, specificity, PPV, and NPV of anti-MCV antibody at different cutoff levels.

Cutoff value	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Youden's index
20 U/ml	97.1	45.5	69.0	92.5	0.43
30 U/ml	78.2	93.4	93.7	77.4	0.72
40 U/ml	72.9	96.3	96.1	74.0	0.69

PPV/NPV: positive/negative predictive value; MCV: mutated citrullinated vimentin.

(81.2%), but also higher specificity (92.0%). Further, when anti-MCV antibodies were present in conjunction with anti-CCP2, it yielded higher diagnostic power in specificity (97.8%) than the double-positive of anti-MCV and RF (96.3%). It is well known that the 1987 ACR revised criteria for classifying RA have limitations, particularly in early RA³. ACR criteria have 91%–94% sensitivity and 89% specificity for established RA, while the sensitivity is even lower for people with early RA²⁸. Therefore, it is urgent to find more sensitive and specific markers for patients with early RA. Anti-MCV deserves attention because it would effectively increase the diagnostic power of serologic tests, especially when it is combined with anti-CCP2.

Our study suggests that there is a certain correlation between anti-MCV and anti-CCP2 in patients with early RA. This indicates that the target antigens of anti-MCV and anti-CCP2 may have some shared epitopes, or one of the physiological targets of anti-CCP2 may be citrullinated vimentin²³.

Further, we evaluated the associations between anti-MCV and clinical or laboratory variables of RA. Anti-MCV showed no significant statistical correlation with mostly clinical and laboratory factors such as ESR, CRP, AKA, APF, global VAS, IgA, IgG, IgM, C3, C4, HRFIgA, and HRFIgG. Anti-MCV antibody concentrations have also been reported as correlated with DAS28, prognostic for disease severity. Being treatment-sensitive, anti-MCV antibody was also reported to be useful in monitoring response to therapy^{23–25}. However, in our study, while DAS28 mean titers of the anti-MCV-positive group were higher than in the negative group, no association was found between circulating levels of anti-MCV and DAS28. This is probably because anti-MCV determination did not take place at the beginning of the disease, and early establishment of treatment might have modified the DAS.

We also found an inferior but important correlation between anti-MCV and radiological assessment ($r = 0.349$, $p = 0.05$, 2-tailed). Remarkably, anti-MCV-positive patients with early RA already had more severe radiographic damage than anti-MCV-negative patients with early RA. Mathsson and colleagues²⁵ reported that, although radiographic scores did not differ between anti-MCV-positive and anti-MCV-negative patients at the investigated time-points, analysis of the change in Larsen score showed faster rates of radiographic destruction in anti-MCV-positive than

in anti-MCV-negative patients, between baseline and 2 years and especially between 1 year and 2 years. With regard to radiographic progression, the patients with RA who were anti-MCV-positive showed more severe bone erosion and joint space narrowing according to the Sharp-van der Heijde method. Further prospective studies are needed to find out whether anti-MCV has the same predictive value for RA as anti-CCP2.

We believe that the anti-MCV antibody assay is a very valuable tool for the diagnosis of early RA. It has superior sensitivity compared with anti-CCP2 and RF. Moreover it may be more useful if the anti-CCP2 assay is performed concomitantly. The combined application of anti-CCP2 and anti-MCV tests can improve the laboratory diagnosis of early RA, thus promote timely treatment.

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