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Evaluation of anti-mutated citrullinated vimentin antibodies, anti-cyclic citrullinated peptide antibodies in patients with rheumatoid arthritis in comparison with other rheumatic diseases; a nephrology point of view

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) is one of the most common autoimmune rheumatic disease with a chronic and progressive inflammatory disorder manifestations leading to articular cartilage damage, and disability, and also renal involvement. It seems that recruitment of tests based on high specific and sensitive serological immunobiomarkers removes these mentioned gaps. Additionally, the results of laboratory tests, assist to reach an accurate prognosis and real estimation of the patient's clinical statue especially hospitalized individuals in intensive care units.

Objectives: The aim of this study is assessment and titration of some autoantibodies as anti-mutated citrullinated vimentin (anti-MCV), anti-cyclic citrullinated peptides (anti-CCP), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in RA patients in comparison to patients with other forms of rheumatologic diseases.

Patients and Methods: This descriptive study was conducted from January to June 2012 in Zanjan province on 100 patients with RA and 100 patients with other rheumatic disease that were randomly selected. All necessary data of clinical history for the patients was extracted from their medical records. After delivering antecubital venous blood (7 mL) to hematology ward of laboratory, quantative ELISA test was performed for autoantibodies.

Results: Anti-MCV tests showed 72% positivity in RA group compared to 10% positivity in other group of rheumatic diseases. There was a significant correlation between positivity of anti-MCV and RA disease. Mean anti-MCV titer is 236.23 ± 2.319 U/mL in RA group and 28.75 ± 0.432 U/mL in other disease group. In this study anti-MCV antibodies had diagnostic sensitivity of 81.7% (versus anti-CCP), diagnostic specificity of 72.22%, positive and negative predictive value 93.05% and 46.42%, respectively.

Conclusion: According to results of this study, not only anti-MCV measurement but also anti-CCP assist to early diagnosis of RA. Results of the recent study could not show definite correlation between anti-MCV and disease activity. The result of this study may be helpful for renal involvement in RA patients, whereas evaluation on this aspect of RA patients seems essential.

Implication for health policy/practice/research/medical education:
According to immunological manifestations of rheumatoid arthritis (RA) and occurrence of renal disorder in some RA patients, serological immunobiomarkers help to accurate diagnosis and follow up of clinical course of this disease.

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Original

Introduction

Rheumatoid arthritis (RA) is one of the most common autoimmune rheumatic disease of an ambiguous and complicated etiology characterized by a chronic, multi-systemic and progressive inflammatory disorder affecting synovial joints (1,2), leading to functional capacity diminution, articular cartilage damage (3-5), deformity, disability and substantial economic costs (6-9). The global prevalence of RA ranges between 0.5%-1% varies upon gender, population and ethnicity mostly in developing countries in young women and elderly people (3,5,10). Above all, due to the aggressive nature and severity of the clinical manifestations of the disease process, also inaccuracy in the RA early diagnosis after symptoms onset, it is potentially recommended to differentiate between persistent RA and other forms of rheumatic diseases; while early diagnostics and prognostics approaches leads to prevent unwanted irreversible joint damages (8,11,12). For long times, diagnosis of RA has been established on radiological manifestations of the diseases. Rheumatoid factor (RF) test is applied routinely in laboratories for RA diagnosis. RF is an auto-antibody (chiefly low affinity IgM type) against the FC portion of IgG immunoglobulin molecule that serological basis for this factor is agglutination method. This factor is not a specific sensitive immunobiomarker and is detectable in other rheumatic diseases, chronic inflammatory conditions, Sjögren's syndrome and even healthy elderly people. A substantial correlation has been observed between RF positivity and disease progression. This factor is routinely found in 50%-80% of RA patients and quantified by sandwich ELISA method (3,7,8,12-14).

Many efforts have been made for a proper RA diagnosis route. A number of autoantibodies associated to RA have been clarified. It is demonstrated that autoantibodies such as anti-perinuclear factors (APFs), anti-keratin antibodies (AKAs), anti-RA33 antibodies, antibodies against several specific antigens, including type II collagen, fibrinogen and α-enolase displayed their challenging insufficiency in terms of specificity and sensitivity than others (9,15-18). Although many attempts have been done for RA diagnosis, new serological markers are still required. Circulating non-RF antibodies have been considered to be of potential diagnostic value with more significant specificity and sensitivity (6,15-18).

Instead, the current laboratory diagnostics of RA particularly early RA, is based on a highly specific markers such as anti-citrullinated proteins/peptides antibodies (ACPA). They have more specificity (94%-99%) and reasonable sensitivity (66%-88%) than RF, in addition of prognostic relevance, high predictive value in progression rate of the disease and disease activity (19-22). These large family glitter as one of the promising diagnostic markers for early onset of RA according to the 2010 ACR/European League against Rheumatism criteria for diagnosis and outcome prediction purposes at RA field (23-26). Also, several members of this autoantibody family have been postulated to play a role in RA pathogenesis, disease duration, prognostic implication for renal involvement in the course of RA and presence of HLA shared epitopes (27-31).

A functional member of this family is anti-cyclic citrullinated protein (anti-CCP) antibody, which is now another most commonly used laboratory test for RA diagnosis and as most widely used members of ACPA particularly in adults. Cyclic citrullinated protein/peptides (CCP) are purified proteins containing modified arginine residues (citrulline), serve as antigen. Anti-CCP is now used as a classification criterion of RA with 96-99% specificity. This autoantibody, due to the appearance before clinical symptoms of RA, validates initial immune dysregulation before disease manifestation. The positive test for anti-CCP may predict the transformation of undifferentiated arthritis into RA (6,20,26,32).

The probability of developing RA from undifferentiated arthritis in patients with positivity in anti-CCP is 90%, whereas 30% in those with negative test (33). In a study, the positive predictive value for RA progression was 80% and this was increased when two or three other tests were used together. Several studies suggest that combination of anti-CCP with RF may yield better to reach an efficaciously optimum diagnosis. Another advantage of anti-CCP positivity is in RF seronegative patients in particular at early stages of the disease (6,34,35).

In recent years, studies have been focused on anti-mutated citrullinated vimentin (anti-MCV) antibodies because of a higher diagnostic value in comparison with anti-CCP and RF (26).

Anti-MCV is another member of ACPA family, reacting with vimentin, which acts as carriers for citrulline hapten. Citrullination is a post-translational modification of arginine residues which is generalized in the RA patient's synovium (36-39). There are many studies have compared anti-MCV and anti-CCP for their diagnostic value in RA, declaring 80% sensitivity. Anti-MCV chiefly associates with higher levels of the disease activity score (DAS28) (40) and joint damages. This accelerates early diagnosis, reliable progression follow up, assessment of functional disability, and response to drug therapy (27,41-45).

In some studies, it is demonstrated that anti-MCV antibodies may be precious factor for RA diagnose in anti-CCP-negative patients. Moreover, anti-MCV antibodies could be practical in monitoring the effects of infliximab therapy and also in RF and anti-CCP negative juvenile idiopathic arthritis patients (46-50), as well as a potential predictor for RA associated lung diseases or even renal involvement. In addition, due to a lower false positivity of the anti-CCP in hepatitis C infected patients which may present arthralgia or synovitis. Hence, this factor (anti-MCV) can be recruited for RA diagnosis for these individuals (51-53). Thus, it is suggested that combination of anti-MCV, anti-CCP and RF are significant for early screening of RA (32).

Objectives

According to above information, the purpose of this study

was to assess the titration of four factors including anti-CCP2, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and anti-MCV in a group of Iranian patients with RA and other rheumatic diseases.

Patients and Methods

Patients

This cross-sectional study was conducted from January to June 2012, at Valiasr Rheumatology Clinic, Zanjan, Iran. One hundred patients with clinically active RA were randomly selected and enrolled, who met the ACR 1987 classification criteria. The duration of RA ranged from 6 months to 6 years for them was registered. All patients were treated with prednisolone, hydroxychloroquine and methotrexate. None of them, received biologic agent therapy. Also 100 subjects were recruited as control including patients with other rheumatic diseases (SLE, Behcet's disease and seronegative arthritis).

DAS28 ≤2.6 was considered inactive disease, 2.6-3.2 as mild, 3.2-5.1 moderate and more than 5.1, high for disease activity.

Laboratory methods

Participants were recruited to come to the laboratory. From the total 200 subjects, 7 mL of peripheral venous blood was withdrawn aseptically by an authorized supervisor with sterile gauge needles from each of the two groups and collected in vacutainer blood collection tubes containing sodium heparin. Around 3 mL of collected blood were left to clot for 15 minutes, then centrifuged. After centrifugation, sera were put into aliquots and stored at -20°C until assayed for anti-MCV and anti-CCP2 antibodies for both patients and controls groups. Anti-CCP2 and anti-MCV tests were performed on all samples as follow:

The anti-CCP2 test was done by using Euroimmun kit (Lübeck, Germany). Anti-CCP2 antibodies were measured by quantitative enzyme-linked immunosorbent assay (ELISA) kit supplies by INOVA Diagnostics (Cat. NO 570139, Lebanon) for the measurement of IgG anti-CCP2 antibodies in patients' sera. The level of greater than 5 RU/mL was considered positive. The CCP2 antigen is bound to the surface of a microwell plate, allowing any present CCP2 antigens bind to the immobilized IgG coating antibodies. A second incubation allowed the enzyme labeled detecting antihuman IgG bind to any patient antigens that have been attached to the microwells and formed a complex. After washing the unbound enzyme labeled anti-human IgG, the remaining enzyme activity was measured by adding a chromogenic substrate. Next to adding stop solution for color development inhibition, measuring the intensity of the yellow color was done by a spectrophotometric ELISA reader. A titer above 20 units was considered as positive.

The anti-MCV antibodies test was done, using Orgentec Diagnostika kit (GmbH, Mainz, Hamburg Germany) according to the manufacturer's instructions. Serum samples were diluted 1:100 and incubated on MCV coated microtiter wells for 30 minutes at room temperature. Plates were washed three times and incubated with peroxidase-labeled detecting anti-human IgG-conjugate for 15 minutes. After washing and substrate addition, microplate was incubated for 15 minutes. Color development was stopped with HCl 1M solution, and the optical density (OD) was measured. Results were expressed in U/mL using a simple point-to-point curve-fitting method. Values of 20.0 IU/mL or greater were considered to be abnormal according to manufacturer's recommendations. In all 100 RA patients, DAS28 was calculated.

ESR tests were measured by the Westergren method. Serum CRP concentrations were determined by immune nephelometry methods on a Turbox nephelometer (Orion Diagnostica, Finland). The titer of 6 mg/L was considered positive for CRP.

Ethical issues

The research followed the tenets of the Declaration of Helsinki; informed consent was obtained. This study was approved by the Ethics Committee of Zanjan University of Medical Sciences (Ethical code# 12/91-602-01).

Statistical analysis

Data were analyzed using SPSS version 18 (SPSS Inc, USA). Descriptive results are shown as number, percent, mean and standard deviation (SD). For comparing the results, the quantitative variables were analyzed with independent *t* test and qualitative variables with chi-square test. Fisher's exact test was also applied. Sensitivity, specificity, correlation coefficient and measure of agreement (Kappa) was determined. Statistical significance was considered when $P<0.05$.

Results

Table 1 indicates demographic information of all patients. Of 100 patients with RA, 73 were females (73%) and 27 were males (27%). The control group consisted of 40 males (40%) and 60 females (60%). The mean ± SD age of patients was 44.89 ± 1.427 years in RA group (range 18-74 years old) and 34.89 ± 1.219 years in the control group (range 13-70 years old) (Table 1).

In the RA group, distribution of positive cases according to DAS28 was recorded 33 patients (22%) in remission, 21 (14%) mild disease activity, 69 (46%) moderate activity and 27 (18%), high activity.

In the RA patients group, anti-MCV was positive in 72 cases (72%) of RA and 10 cases (10%) of controls. Chi-

Table 1. Demographic information of patients and control group

Demographic parameters	RA patients n = 100	Control group; other rheumatic disease n = 100	P value
Age (y)	44.89 ± 1.427	34.89 ± 1.219	0.264
Gender			0.221
Female	73	60	
Male	27	40	

square test revealed a statistically significant relationship between anti-MCV positivity and RA diagnosis. Notably, more frequency of anti-MCV positivity was observed in RA group than to other (Table 2).

The results also showed that the anti-MCV titer mean in the RA group is statistically higher than other rheumatic diseases (236.23 ± 2.32 U/mL and 28.75 ± 0.432 U/mL respectively; $P < 0.001$).

Table 3 represents the frequency distribution of anti-MCV positivity in other rheumatic disease. There was no significant statistical difference between anti-MCV positivity and each of three other rheumatic diseases.

Table 4 shows anti-CCP and anti-MCV positivity for RA group. 67% of cases were simultaneously anti-CCP and anti-MCV positive and 13% anti-CCP and anti-MCV negative. Table 4 displays sensitivity and specificity of anti-MCV in comparison with anti-CCP tests (sensitivity = 0.82 and specificity = 0.72). In RA patients group, both anti-CCP and anti-MCV were negative in 13 cases, while positive anti-CCP and negative anti-MCV were detected in 15 cases and negative ACCP and positive anti-MCV seen in 5 cases. The kappa measure of agreement was 0.810 for these results. The kappa coefficient for ACCP and anti-MCV was calculated at 0.443 (0.21-0.61).

Figure 1 shows statistically significant correlation between anti-CCP and anti-MCV titer in RA patients ($P = 0.001$).

Figures 2 and 3 show reverse correlation between anti-MCV and CRP/ESR titers in RA patients.

Table 5 shows correlation between anti-MCV titer and CRP and ESR in RA and control group which is not statistically significant according to coefficient correlation.

Table 6 shows relation between anti-MCV titer, CRP and ESR in both study groups.

Table 2. Distribution of anti-MCV tests results in RA patients and in patients with other rheumatologic diseases

Anti-MCV	Study groups		*P* value
	RA patients (n = 100)	Patients suffering other rheumatic disease (n = 100)	
Positive	72 (72%)	10 (10%)	0.001
Negative	28 (28%)	90 (90%)	0.001

Table 3. Anti-MCV positivity in other rheumatologic diseases subgroups

Anti-MCV	Seronegative arthritis	SLE	Behcet's diseases
Positive	4 (40%)	6 (60%)	0 (0%)
Negative	54 (60%)	29 (32.2%)	7 (7.8%)

Table 4. Anti-MCV in comparison with anti-CCP tests results in RA patients

Anti-CCP	Anti-MCV		*P* value
	Positive	Negative	
Positive	67 (67%)	5 (5%)	0.001
Negative	15 (15%)	13 (13%)	

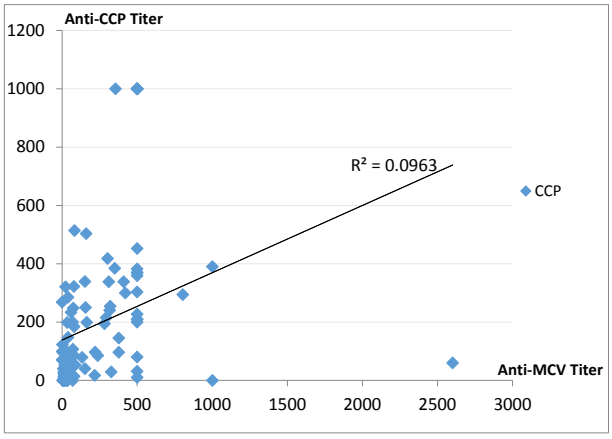

Figure 1. Correlation between anti-CCP and anti-MCV titer in RA patients.

Discussion

In this study, we compared the diagnostic values of anti-CCP and anti-MCV. The aim of this study was to distinguish more informative test for diagnosing RA. Previous studies yielded controversial results without a definite agreement to conclude a more accurate test. There is also no comprehensive study in an Iranian cohort of RA patients.

On the other hand, it is obvious that, totally, mentioned immunoserological factors (anti-MCV and anti-CCP), are the result of an immune response to an identified antigen. In addition to RA, increased concentrations of circulating soluble immune complexes are highlighted in several pathological situations such as systemic lupus erythematous, chronic inflammatory bowel diseases (IBD), various forms of glomerulonephritis and even disseminated malignancies (54).

Glomerulonephritis and renal co-morbidities are one of the frequent, but not well recognized and diagnosed, manifestations of the RA. It is demonstrated that repeatedly administration of antigen leads to chronic nephritis, as an important causes of death subsequent to chronic infections. Additionally, other complications such as vasculitis due to immune complexes deposition, aggregation and activation of complement system components, release of some enzymes and kinin. The prevalence of these kidney disorders ranges from 5% to 50% in RA patients. In addition, variation in the antigen size, immunoglobulin classes and antigen antibody ratio are significant determinants in localization or expansion of the disease (54,55).

Hence, with a nephrologic point of view, we decided to generalize our results for medicine specialists to reach an accurate prognosis and real estimation of the patient's clinical statue especially at intensive care units.

In a study by Hurkmans et al, for progression prediction of the disease from undifferentiated arthritis to RA, the anti-CCP test had presented very good specificity and PPV. Anti-MCV did not seem to be more informative, and adding RF and anti-MCV tests to anti-CCP2 did not enhance the diagnostic value of the laboratory test and it is

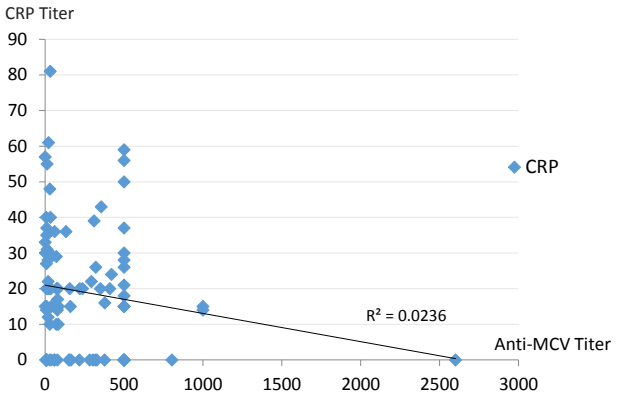

Figure 2. Correlation between anti-MCV and CRP titers in RA patients

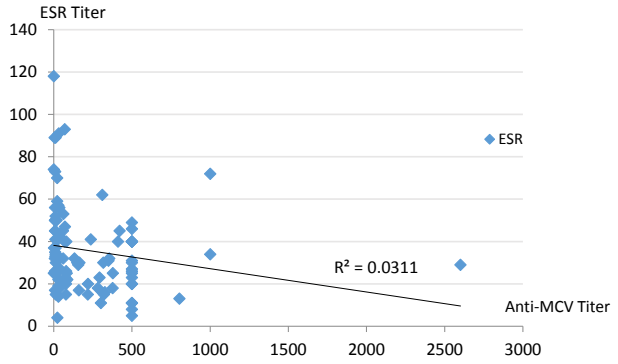

Figure 3. Correlation between anti-MCV and ESR titer in RA patients.

Table 5. Relationship between anti-MCV titer and CRP and ESR in study groups

Variables	Anti-MCV titer		*P* value
	Other rheumatic disease, n = 100	RA patients, n = 100	
ESR (mg/L)	39.5±2.15	43.95±8.98	< 0.001
CRP (mm/h)	17.28±1.48	19.22±1.71	< 0.001

Table 6. Pearson's correlation test between anti-MCV titer and CRP and ESR in study groups

Variables	Pearson's correlation		*P* value	
	RA	Other rheumatic disease	RA	Other rheumatic disease
ESR (mm/h)	0.09	0.12	0.220	0.356
CRP (mg/L)	0.12	0.12	0.226	0.127

concluded that a single test was efficient (54).

High specificity, more than 90% PPV for ACCP and a poor outcome for ACCP positive RA patients were reported in a review published in 2009 (55). In a recent meta-analysis, 16 studies on anti-MCV were analyzed. Sensitivity, specificity, positive likelihood rate (LR), negative LR and diagnostic odds ratios (ORs) were estimated to be 0.77, 0.89, 7.24, 0.28 and 29.66 respectively (14).

In another study, sensitivity of anti-MCV was reported to be 79.6% and specificity 96.6%. They detected that test positivity was accompanied with a higher DAS28 (56). In addition, this finding has been confirmed by Syversen et al, who reported more advanced joint damage in patients with anti-MCV positivity (57).

In most of researches, the sensitivity of anti-MCV was somehow higher than anti-CCP, but anti-CCP was more specific (34,56,58,59). The similar results have been demonstrated in another studies while investigators found that in RF negative patients, the sensitivity of anti-MCV is high (43.8% versus 30%) (56).

Our study did not show obvious differences between sensitivity and specificity of anti-CCP and anti-MCV (sensitivity 85%, 81%, specificity 96% and 95%, respectively). The analysis of the above results displayed kappa of high agreement between these two tests (kappa = 0.81), and correlation coefficient of 0.63 ($P = 0.001$) which means that both tests have similar value. In other words, anti-CCP and anti-MCV positivity usually coincide.

In the study of Arnett et al, a significant correlation between anti-MCV and ACCP was seen (60). However, in our study, in a small proportion of our cases, this result was not accurate, while 10 cases (6.7%) had positive anti-CCP and negative anti-MCV, and four cases (2.7%) had negative anti-CCP and positive anti-MCV. It was slightly different in the study of Majithia et al in which the proportion of positive anti-MCV in ACCP cases was equal to the proportion of positive ACCP in anti-MCV negative patients (61).

In ROC analysis, the level for each test with 100% specificity was determined. This was 9.8 U/mL for anti-CCP (2 times of the laboratory cut-off point) and 89.5 U/mL for anti-MCV (4 times of the laboratory cut-off point). The sensitivity of the tests was 81% and 57%, respectively. The latter means that anti-CCP with the level of 2 times more than normal and 81% sensitivity is specific for diagnosis of RA. However, for anti-MCV, this level is four times more than normal with a sensitivity of 57%. Below these levels, anti-MCV has less specificity. This might be a reason that anti-MCV has been introduced as a new biomarker for diagnosis of ankylosing spondylitis (62). Positive anti-MCV was also reported in SLE, Sjögren's syndrome, psoriatic arthritis, Epstein-Barr virus and hepatitis C virus infected patients (56,59). Because of low proportion of non-RA controls in our study, we obtained these results.

Conclusion

As a whole, we came to this conclusion that the titer of anti-MCV in RA patients are significantly higher, comparing to the other autoimmune diseases as systemic lupus erythematous, Behcet's disease, seronegative arthritis. Furthermore, the high sensitivity of anti-MCV in RA diagnosis, beside of anti-CCP which has a great specificity in diagnosis of RA, can be helpful in differentiation of RA from other types of arthritis.

Limitations of the study

This is a single center study with a limited proportion of patients. We strongly suggest larger studies on this aspect of RA.

Authors' contribution

AS, AP, and MM acted as rheumatologist specialist advisor, nephrologist specialist advisor, and oncologist advisor, respectively. In addition, AS did literature review and clinical improvement. KK performed statistical analyses. ARE contributed as corresponding author to conceptualization, study design and project administration, data interpretation helps, revision, edition and approvement of final version of manuscript. MN organized data collecting, literature review, and scientific writing.

Conflicts of interest

The authors declare no conflict of interest.

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