Differentiation between Rheumatoid Arthritis and Chronic Hepatitis C Virus Associated Arthropathy among Egyptian Patients; Does Anti-Mutated Citrullinated Vimentin Have A Role?

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Abstract: Aim of the work: to study the role of anti-mutated citrullinated vimentin (anti-MCV) in the differentiation between Rheumatoid arthritis (RA) and hepatitis C virus (HCV)-associated arthropathy among Egyptian patients. **Patients and Methods:** This study was conducted on two groups of patients. Group I included 25 RA patients. Group II included 25 patients with chronic HCV -associated arthropathy. Group III included 20 healthy individuals who served as a control group. Clinical Assessment included DAS 28.Laboratory investigations included rheumatoid factor (RF), anti- cyclic citrullinated peptide (anti-CCP Ab), and anti-mutated citrullinated vimentin (anti-MCV). **Results:** Articular involvement among HCV–associated arthropathy patients showed 9/25 (36%) patients presenting with symmetric RA-like polyarthritis. Anti-MCV was positive in 20 (80%) of RA patients and in 8 (32%) of HCV patients. There was a statistically significant difference between RA and HCV-associated arthropathy patients as regards the positivity of anti-CCP and anti-MCV (P<0.001) and (P=0.001) and also as regards the levels of anti-CCP and anti-MCV (P<0.001). Anti-MCV was significantly positively correlated with DAS 28 among patients with RA(r=0.826,P<0.001) and with viremia among patients with HCV associated arthropathy (r=0.511, P<0.01). Anti-MCV was significantly correlated with the level of Anti-CCP(r=0.664,P<0.001).ROC curve showed that the sensitivity, specificity and accuracy of anti-MCV in RA to be 80%, 80%, 84% respectively while for Anti-CCP it was 80%, 96%, 86% respectively. Multiple regression analysis between Anti-MCV and Anti-CCP as independent variables to predict RA as a dependent variable showed a non-significant effect of Anti-MCV, while a significant effect was elicited of Anti-CCP (P<0.05). **In conclusion,** it seems that anti-CCP is more specific and could have a better role than anti-MCV in differentiating RA patients from chronic HCV- associated arthropathy patients.
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Key words: rheumatoid arthritis, hepatitis C, arthropathy, and anti-mutated citrullinated vimentin

1. Introduction:

Egypt has the highest prevalence of HCV in the world. The national prevalence rate of HCV antibody positivity in Egypt has been estimated to be between 10-13% **(Mohamed, 2004)**[1].

HCV-related arthritis is one of the extrahepatic manifestations of HCV. It commonly presents as symmetrical inflammatory arthritis involving small joints. The joints involved in HCV-related arthritis are similar to rheumatoid arthritis (RA). HCV-related arthritis is usually non-deforming and there are no bony erosions in the joints **(Kessel *et al.*, 2000)**[2]. RA-like HCV-related arthropathy can be clinically indistinguishable from RA itself. Thus, differentiating patients with HCV-related symmetric polyarthritis from patients with RA represents both a diagnostic and a therapeutic challenge **(Bombardieri *et al.*, 2004)** [3].

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of undetermined etiology involving primarily the synovial membranes and articular structures **(Moreland and Curtis, 2008)**[4].

Serological diagnostic testing is of growing importance in the detection and differentiation of RA. Apart from the traditional detection of the rheumatoid factor (RF), new specific autoantibodies to citrullinated antigens have made a crucial contribution to the diagnosis of RA **(Egerer *et al.*, 2009)** [5].

It is difficult to differentiate between true RA and HCV patients with positive rheumatoid factor but without RA. Antibodies to citrullinated peptides have been postulated as good candidates for diagnosing RA. Vimentin is an intermediate filament that is widely expressed by mesenchymal cells and macrophages. Modification of the protein occurs in macrophages undergoing apoptosis, and antibodies to citrullinated vimentin (anti-MCV) emerge if the apoptotic material is inadequately cleared **(De Ryke *et al.*, 2005)** [6].

Extra-hepatic complications can vary between populations, possibly due to genetic and viral factors, such as viral genotype. RA-like HCV-related arthropathy can be clinically indistinguishable from recent- onset RA, in which articular damage and deformities have not yet occurred. Studies on RA patients found that anti-MCV antibodies have the same specificity as anti-CCP antibodies, but with

better sensitivity (82% versus 72%) **(Bang *et al.*, 2007).**

Aim of the Work:

The aim of our work was to study the role of anti-MCV antibodies in the differentiation between RA and chronic hepatitis C virus associated arthropathy among Egyptian patients.

2. Patients and Methods:

This case-control study was conducted on two groups of patients recruited from the Physical Medicine, Rheumatology and Rehabilitation and Internal Medicine outpatient clinics of Ain Shams University hospitals. Group I included 25 RA patients diagnosed according to the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) new classification criteria for RA ***(Aletaha et al., 2010)***[8] and negative for anti-HCV antibodies. Group II included 25 patients with chronic HCV -associated arthropathy positive for HCV antibody in serum using a Microparticle Enzyme Immunoassay (MEIA) test, with the Abbot AxSYM (Chicago, IL, USA) and HCV RNA using a quantitative reverse transcriptase polymerase chain reaction technique (RT-PCR), (Promega Co., Madison, WI, USA). The detection limit was 100 IU/ml; weak viremia (< 100.000 IU/ml), moderate viremia (>100.000–1000.000 IU/ml), severe viremia (> 1000.000 IU/ml). Group III included 20 healthy individuals matched for age and sex who served as a control group were included for comparative assessment of the investigated serological disease markers.

Exclusion Criteria

-Patients with other connective tissue disease
-Patients positive for HBs Ag.
-Patients with chronic infection/inflammation
-Patients with malignancy
-Patients with organ transplant

Clinical Assessment

Patients had full history taking including the history of known disease duration and thorough clinical examination including BMI (Kg/m^2). For RA patients; we assessed DAS 28 ***(Preevo et al., 1995)***[9]. Mild disease activity was assigned to patients with score of ≤ 3.2 moderate was>3.2 to ≤ 5.1,and high activity was >5.1. For HCV- associated arthropathy patients we assessed pattern of articular affection.

An informed written consent was obtained from all participants and the local ethics committee approved the study.

Laboratory investigations including rheumatoid factor (RF) using latex technique. Anti cyclic citrullinated peptide (anti CCP Ab) by ELISA technique using the QUANTA Lite ™ CCP IgG INOVA Diagnostics, San Diego, CA 92131,USA. A titre above 20 U/ml is considered positive.

Measurement of serum anti-MCV antibodies in patients (RA and HCV patients) and control groups using an indirect solid phase enzyme immunoassay (ELISA) kit with STAT FAX 2100 apparatus for the quantitative measurement of IgG class autoantibodies against mutated citrullinated vimentin (MCV) in human serum (The kit was provided by ORGENTEC Diagnostika GmbH Carl-Zeiss-Straße 4955129 Mainz-Germany). (http:// www. hcmed. net/ orgentecdiagnostika- gmbh). Anti-MCV IgG [U/ml] positive: > 20 U/ml.

Statistical analysis was used using SPSS version 18; Student *t* test was used for comparison between two groups(parametric data),Chi - square for comparison as reaagrds qualitative data,ANOVA for comparison between more than two groups (parameteric data), Mann-Whitney test for comparison between two groups (non-parametric data),Kruskal-Wallis for comparison between more than two groups (non-parametric data). ROC curve was used to test for the sensitivity,specificity and accuracy to best value.Spearman's correlation coefficient (*r*) was used to test correlation between quantitiative variables (non-parameteric data) and Multi-regression analysis was used for non-parametric data to search for the independent parameters that can predict the targer parameter (dependent variable).

P- value >0.05: non-significant
P-value <0.05:significant

3. Results:

Demographic and clinical data of the studied groups are shown in **Table (1).**

Articular involvement among HCV–associated arthropathy patients showed 9/25 (36%) patients presenting with symmetric RA-like polyarthritis. The metacarpophalangeal and the wrist joints were the most frequently involved. The remaining 16/25 (64%) showed evidence of polyarthralgias involving the metacarpophalangeal, wrist, elbow and knee joints.

Among RA patients; 1 patient (4%) had mild disease activity, 10 (40%) had moderate disease activity, while14 (56%) had severe disease activity. Among patients with HCV-associated arthropathy; 13 (52%) had mild viremia,8(32%) had moderate viremia and 4(16%) had severe viremia.

RF was positive in 19(76 %) of RA patients and in 11 (44%) of HCV patients. Anti CCP was positive in 20(80%) of RA patients and in 2(8%) of HCV patients. Anti-MCV was positive in 20 (80%) of RA patients and in 8 (32%) of HCV patients. There was a statistically significant difference between patients with RA and HCV–associated arthropathy as regards the percentage of patients with positive RF, patients with positive anti-CCP and patients with positive

anti-MCV; (P<0.05), (P<0.001) and (P=0.001) respectively **(Table 2).**

There was a statistically significant difference (P<0.001) between patients with RA and HCV-associated arthropathy as regards the levels of anti-CCP and anti-MCV as shown in **(Tables 3&4).**

The level of Anti-MCV was not correlated with age (r=0.083, P >0.05), BMI(r=0.126,P>0.05), or disease duration (r=*0.273,P*>0.05) Anti-MCV was significantly positively correlated with DAS 28 among patients with RA (r=0.826, P<0.001) and with viremia among patients with HCV associated arthropathy (r=0.511, P<0.01). Anti-MCV was significantly correlated with the level of Anti-CCP (r=0.664,P<0.001) as shown in **(Table 5).**

ROC curve analysis to assess the reliability of Anti-CCP and Anti-MCV to distinguish RA from HCV-associated arthropathy showed area under ROC curve was 1.129 (95%confidence interval (CI), 1.024 to 1.246 for Anti-CCP while it was 0.999 (95% CI 0.988 to 1.009) for Anti-MCV. Their sensitivity, specificity and accuracy was (80%, 96%, 86% respectively) for Anti-CCP at best cut-off value of 22 IU/ml and (80%, 80%, 84% respectively) for Anti-MCV at best cut-off value of 30 IU/ml as shown in **(Figures1&2).**

Table (1): showing comparison between the studied patients and controls as regards demographic and clinical data.

	Group I (RA patients) N=25	**Group II (HCV-patients) N=25**	**Group III (Controls) N=20**	**F/*t*/X^2**	***P-value***
Age (years) Range (mean ±SD)	 23-63 (37.5±10.4)	 24-64 (38.5±11.4)	 25-52 (39.1±8.6)	0.136	0.87 (NS)
Sex F: M	22:3	21:4	14:6	2.428	0.297 (NS)
BMI (Kg/m^2) Range (mean ±SD)	 19-45 (30.24±6.75)	 20-47 (29.8±6.65)	 19-33 (27.4±4.21)	1.351	0.266 (NS)
Disease duration (months) Range (mean ± SD)	 5-36 (18.56±9.87)	 5-48 (20±11.899)		-0.466	 0.64 (NS)
DAS 28 Range (mean ±SD)	 3-7.4 (5.44±1.243)				

BMI=body mass index, DAS 28=disease activity score 28,NS =non-significant

Table (2): showing the percentage of patients with positive anti-CCP and positive anti-MCV among Group I and Group II patients.

	Group I (RA patients) N=25	**Group II (HCV patients) N=25**	***t***	***P-value***
RF	19 (76%)	11 (44%)	5.333	0.021 (S)
Anti-CCP positive (%)	20 (80%)	2 (8%)	26.299	<0.001 (S)
Anti-MCV Positive (%)	20 (80%)	8 (32%)	11.688	0.001 (S)

RF=Rheumatoid Factor, Anti-CCP =anti cyclic citrullinated peptide, Anti-MCV =anti mutated cirullinated vimentin, S=significant, HS=highly significant

Table (3): showing comparison between Group I and Group II patients as regards the level of Anti-CCP.

	Anti-CCP				**Mann-Whitney Test**	
	Range	**Median**	**Interquartile Range**	**Mean Rank**	**Z**	***P*-value**
Group I (RA patients)	3.500-280.000	65.000	236.500	34.540	-4.390	<0.001 (S)
Group II (HCV patients)	2.800-25.000	13.000	11.250	16.460		

Anti-CCP = Anti-cyclic citrullinated peptide, HS =highly significant

Table (4): showing comparison between Group I Group II patients as regards the level of Anti-MCV.

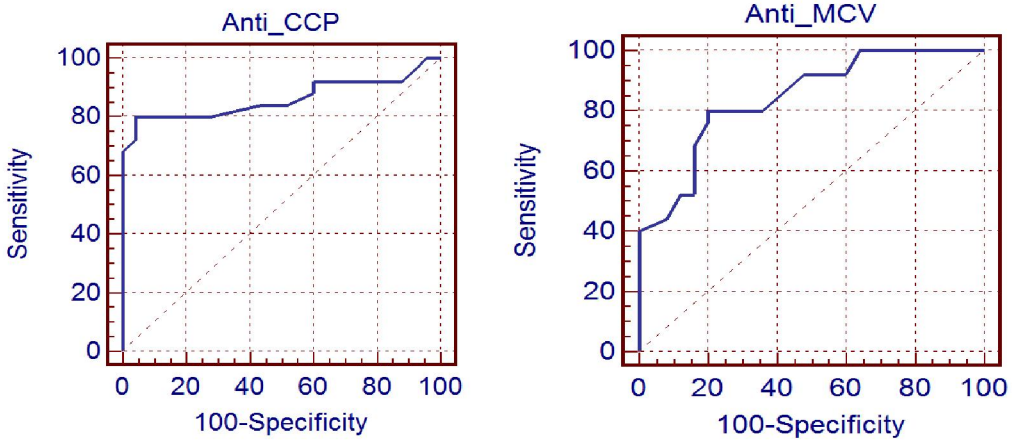
	Anti-MCV				Kruskal-Wallis Test	
	Range	Median	Interquartile Range	Mean Rank	X^2	*P*-value
Group I (RA patients)	16-800.0	200.000	559.000	53.800	40.359	<0.001 (S)
Group II (HCV patients)	6.0-300.0	17.000	13.500	33.380		
Controls	3.0-18.00	10.000	4.000	15.275		

Anti-MCV=anti-mutated citrullinated vimentin, HS =highly significant

Table (5): showing the correlation between anti-MCV and the different studied variables.

Correlation	Anti-MCV	
	r	*P*-value
Anti-CCP	0.664	0.000 (S)
Age (yrs.)	0.083	0.569 (NS)
BMI (Kg/m^2)	0.126	0.385 (NS)
Disease duration	0.273	0.055 (NS)
DAS 28	0.826	0.00 (S)
viremia	0.511	0.009 (S)

Anti-MCV=anti-mutated citrullinated vimentin, Anti-CCP = Anti-cyclic citrullinated peptide, BMI=body mass index, DAS 28=Disease activity score, HS =highly significant



Figures 1&2: The sensitivity and specificity of Anti-CCP and Anti –MCV.

Multiple regression analysis between Anti-MCV and Anti-CCP as independent variables to predict RA as a dependent variable showed a non-significant effect of Anti-MCV (*P* =0.791) (*P*>0.05), while a significant effect was elicited of Anti-CCP (*P*=0.015) (*P*<0.05).

4. Discussion:

Owing to the difficulty in clinical differentiation between RA and HCV–associated arthropathy; especially when presenting as symmetric polyarthritis of the small joints of the hands, serological markers have been relied upon including RF, and anti-CCP.

RF detection has been shown to be of limited value.In our study RF was positive in 44% of patients with HCV-associated arthropathy. In previously performed studies it was positive in 61%, 46.7% and 37.5% of patients with HCV- associated arthropathy **(Zukeramn *et al.*, 2000)**[10], **(Bombardieri *et al.*, 2004)** [3] and **(Kaptanoglu *et al.*, 2010)** [11].

Anti-CCP antibodies were reported by most of the studies to be useful in discriminating between RA and HCV-associated arthropathy as it was either not detected in any of the patients with HCV- associated arthropathy **(Bombardieri *et al.*, 2004)** [3], **(Zehairy M *et al.*, 2012)**[12], or present in a very few

percentage (5.6%) **(Sene et al., *et al.*, 2006)**[13]. In our study it was detected in about 8% of HCV associated arhtropathy patients.

Bassiouni and colleagues (2009)[14] conducted a study on Egyptian patients to study the frequency and clinical significance of anti-CCP antibodies in patients with chronic HCV infection, with and without manifestations of joint involvement, compared to RA patients. Anti-CCP antibody level was positive in 70% of RA patients, and in 20% of HCV patients with articular manifestations. They recommended diagnosis of HCV arthropathy in HCV patients based on the absence of anti-CCP antibodies to be interpreted with caution.

Owing to ethnic differences in the results of the use of different serologic markers in the diagnosis of RA **(Al-Shukaili *et al.*, 2012)** [15] and to the questionable value of anti–CCP antibodies in differentiating between RA and HCV-associated arthropathy we conducted our study on anti-MCV to evaluate its role in the differentiation between RA and HCV-associated arthropathy among Egyptian patients.

Anti-MCV was positive in about 80% of RA patients, whereas it was positive in about 32% of HCV-associated arthropathy. There was a statistically significant difference between RA and HCV associated arthropathy patients as regards RF (P<0.05),anti-CCP and anti-MCV (P< 0.001), while

In addition, the median, mean rank and range levels of anti-MCV and anti-CCP were statistically significantly higher in RA than in HCV –associated arthropathy patients (P< 0.001) as supported by (**Liu *et al.*, 2008**)[16] and **(Zehairy *et al.*, 2012)** [12].

In this study, RA patients had no extra-articular manifestations. Different studies found no difference in autoantibodies levels of RA patients with or without extra-articular involvement **(Sghiri *et al.*, 2008)**[17] **and (Kaptanoglu *et al.*, 2010)**[11].

RA disease activity was assessed by DAS-28, which was correlated with anti-CCP and anti-MCV (r= 0.629, r=.826 respectively, P<0.001). In addition, there was no significant difference was found between mild and severe disease regarding different autoantibodies (P>0.05) **(Poulsom and Charles 2008, Ursum *et al.* (2008), and Kaptanoglu *et al.*, 2010)** [18,19,11].

All HCV patients in our study had articular manifestations. Polyarthralgia was frequent (64%). The most frequent joint affection were metacarpophalngeal, wrist, elbow and knee joints as reported by **Kaptanoglu *et al.*, in 2010** [11].

It is well known that autoantibodies may be positive in HCV infection without clinical involvement **(Muratori *et al.*, 2003)** [20]. Anti-CCP was detected in about 8% of our HCV- associated arthropathy patients, although it was negative in another study and retrospectively detected in patients with RA and HCV **(Bombardieri *et al.*, 2004)**[3]. Furthermore, **Bassyouni *et al.*, in 2009**[14] detected anti-CCP in about 8.5% of HCV patients without arthritis and in about 20% of HCV patients with articular manifestations. They suggested that HCV patients with arthropathy could be prone to develop RA.

There was a significant positive correlation between anti- MCV and anti-CCP in RA and HCV patients (r= 0.664, P<0.001). This finding is consistent with (**Mutlu *et al.*, 2009)** [21].

Both anti-CCP and anti- MCV showed a statistically significant correlation with viremia (r=0.411, r= 0.511, respectively, P< 0.01).

Our study found that anti-CCP was more specific (96%) for distinguishing RA and HCV-associated arthropathy patients than anti-MCV (80%) **(Bombardieri *et al.*, 2004, Lienesch *et al.*, 2005, Sene *et al.*, 2008 and Zehairy *et al.*, 2012)**[3,22,12].

In roc analysis, area under curve (AUC) was higher for anti-CCP (sensitivity 80% and specificity 96%) than anti-MCV (sensitivity and specificity 80%).

Anti-MCV has been demonstrated to perform better than anti-CCP as predictor of radiographic damage in RA (**Bartoloni *et al.*, 2012**) [23]. On the other hand, the high rate of anti-MCV detection in infectious diseases (32% in our HCV patients), chronically inflamed tonsillar tissues (**Poulsom and Charles 2008**) [18], besides equal sensitivity of anti-CCP and anti-MCV in our study (80%) and nearly equal in **Zehairy *et al.*, 2012** [12] (anti-MCV 93.3, anti-CCP 96.7%) and about (70% for anti-MCV and 79% for anti-CCP) in another study **(Kaptanoglu *et al.*, 2010)**[11], limits its diagnostic value in differentiation of arthritis.

Sghiri *et al.*, 2008 [17] had investigated the diagnostic performance of anti-MCV in RA including hepatitis C patients as controls. Their results favored specificity of anti- CCP.

It seems that anti-MCV antibodies may be useful in diagnosis of RA, however it has no additional role over anti-CCP in differentiating between RA and HCV- associated arthropathy.

In conclusion, anti-MCV levels are high in RA and it has significant correlation with anti-CCP and disease activity. However, its lower specificity suggested that it should be interpreted with caution especially in HCV- associated arthropathy. It seems that anti-CCP is more specific and could have a role in differentiating RA from chronic HCV- associated arthropathy patients.

5. Conflicts of Interest:

The authors have no conflict of interest to declare.

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