IJMA

INTERNATIONAL JOURNAL OF MEDICAL ARTS

VOLUME 6, ISSUE 11, November 2024

P- ISSN: 2636-4174
E- ISSN: 2682-3780

Available online at Journal Website
https://ijma.journals.ekb.eg/
Main Subject [Rheumatology]

Original Article

The Association Between Anti-Cyclic Citrullinated Peptide and Anti-Mutated Citrullinated Vimentin and The Extra-articular Manifestations in Patients with Rheumatoid Arthritis

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Article information

Received: 01-10-2024

Accepted: 18-11-2024

DOI: 10.21608/ijma.2024.325391.2049.

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Citation: Khafagy HE, Abd El-Wahab HE, Omran TM, Abd El-Aziz TM. The Association Between Anti-Cyclic Citrullinated Peptide and Anti-Mutated Citrullinated Vimentin and The Extra-articular Manifestations in Patients with Rheumatoid Arthritis. IJMA 2024 Nov; 6 [11]: 5055-5061. doi: 10.21608/ijma.2024.325391.2049.

Abstract

Background: Early detection of extra-articular symptoms [ExRA] in RA patients is crucial, and lifesaving. This study examined the relationship between Anti-Cyclic Citrullinated Peptide [Anti-CCP] and Anti-Mutated Citrullinated Vimentin [Anti-MCV] positivity and extra-articular symptoms in rheumatoid arthritis patients

Patients and Methods: The present investigation included 50 rheumatoid arthritis patients: 25 had extra-articular symptoms [group 1] and 25 did not [group 2]. All patients underwent a complete history taking, clinical, and rheumatological assessment, followed by laboratory tests including anti-CCP/anti-MCV measurements.

Results: As regard to anti-CCP, it ranged from 4 to 530 IU/ml; and there was no significant increase in group 1 when compared to group 2. On the other hand, anti-MCV ranged from 8 to 500 IU/ml; and there was statistically significant increase of anti-MCV in group 1 when compared to group 2 [272.44±117.61 vs 91.08±125.71 respectively]. In diagnosing extra-articular manifestations, anti-CCP antibodies had lower predictability [0.72] than anti-MCV antibodies [0.85], which had higher sensitivity [96%], specificity [76%], and cut off point > 90 IU/ml.

Conclusion: Rheumatoid arthritis patients with anti-MCV antibodies exhibited strong extra-articular manifestation predictors. Anti-CCP is a powerful diagnostic marker of rheumatoid arthritis, especially in early stages, but it had no significant connection with extra-articular symptoms.

Keywords: Rheumatoid Arthritis; Anti-Cyclic Citrullinated Peptide; Anti-Mutated Citrullinated Vimentin.

INTRODUCTION

Rheumatoid arthritis [RA] is an inflammatory process. It can affect multiple systems and organs, causing extra-articular symptoms [ExRAs] in men and women of any age [1].

ExRAs are seen in 17.8% to 40.9% of RA patients [2]. These symptoms can impact multiple organs, with 15% severe [3]. The death rate for people with ExRAs is five times higher than those without [4].

ExRAs like vasculitis, pericarditis, pleuritis, amyloidosis, and Felty's disease shorten life expectancy. Cardiovascular illness increases early mortality. RA patients without ExRA have survival rates comparable to the normal population [4-7].

Male gender, severe joint disease, decreased functional ability, higher inflammatory markers, and high RF and ANA titers predict ExRAs. ExRAs are also predicted by smoking, long disease duration, and HLA-DRB1*04-associated rheumatoid arthritis [8].

Multiple ExRAs can occur in one patient due to risk factor combinations. Several severe extra-articular symptoms are connected to rheumatoid nodules [9]. Other autoantibodies have been related to ExRA than RF and ANA. Anti-cyclic citrullinated peptide antibodies are found in 55%–69% of RA patients' serum [10].

Researchers have found conflicting results on the relationship between anti-CCP and ExRA. A previous study found that 77% of ExRA patients had anti-CCP, with a borderline significant difference between ExRA patients and their controls without ExRA[11].

A separate study found 65.3% connection between anti-CCP and ExRA [12].

Anti-CCP did not correlate with ExRA in long-term or early RA patients [13]. A recent study found no link between ExRA and anti-CCP positivity, whereas rheumatoid nodules were slightly correlated with this marker [14].

Recently tested antibodies targeting mutant citrullinated vimentin [anti-MCV] for rheumatoid arthritis diagnosis showed high sensitivity and specificity [15]. However, anti-MCV-ExRA association studies are lacking. A study found no link between anti-MCV or anti-CCP antibodies and ExRA [16].

The present study examined the relationship between extraarticular symptoms and Anti-Cyclic Citrullinated Peptide and Anti-Mutated Citrullinated Vimentin positivity in rheumatoid arthritis patients.

PATIENTS AND METHODS

The present study included 50 patients diagnosed with rheumatoid arthritis. The diagnosis of rheumatoid arthritis was done based on the 2010 ACR/EULAR Classification criteria for early arthritis [17]. Patients were enrolled from the Rheumatology Clinic at Al-Azhar University Hospital in New Damietta. There were 25 patients with extra-articular manifestations [group 1] and 25 patients without extra-articular signs [group 2]. Before participation in this study, the objectives and methods were elucidated to all patients, and informed consent was secured from each participant, in accordance with the protocol of Al-Azhar University Hospital. Our study was guided by the Helsinki declaration principals. Ethical approval was obtained from the institutional review board of our institution. We recruited our patients according to the following criteria:

The inclusion criteria: 1] Male or female patients. 2] Above 18 years of age. 3] Patients with confirmed diagnosis of rheumatoid arthritis. 4] Patients with or without extra-articular manifestations.

The Exclusion criteria: Patients with associated autoimmune disease

Data collection: All patients underwent

1) Comprehensive history acquisition, encompassing

a. Sociodemographic information
b. Duration of the Research Assistantship.
c. Metrics of disease activity [VAS-pain, disease activity score-28, length of morning stiffness].
d. Metrics of illness severity [Health Assessment Questionnaire–Disability Index [HAQ-DI]].

2) Comprehensive clinical assessment:

A) To identify the presence of ExRA via:

- Vital signs: [Temperature, pulse, blood pressure [BP], and respiration rate [RR]]
- Systematic examination: [cardiovascular, pulmonary, neurological, dermatological, ophthalmic, abdominal, and genitourinary systems]

B) Joint assessment:

- **Distribution of shared involvement.**
  - Joint Inflammation: edematous, erythematous, sensitive, febrile
  - Active or passive range of motion
  - Volatility
- **Existence of malformations.**
- **Indicators of disease activity** [tender joint count, swelling joint count, DAS score] • Indicators of disease severity [joint erosion score]

C) Comprehensive Musculoskeletal Assessment: A total of 28 joints, encompassing bilateral glenohumeral, elbow, wrist, metacarpophalangeal [MCP], proximal interphalangeal [PIP], ankle, and knee joints, were evaluated for each patient to ascertain:

D) Assessment of Rheumatoid Arthritis Activity and Severity

Visual Analogue Scale for Pain Evaluation:

It is a 100-mm linear scale that denotes a continuum of pain severity. Verbal anchors are positioned at both ends of the line: 'no

pain' on the left and 'worst pain conceivable' on the right. sufferers were apprised of the utilization of this scale, after which rheumatoid arthritis sufferers were requested to indicate their pain intensity by marking a position on the line. The distance from the left side measures pain intensity [18].

Health Assessment Questionnaire–Disability Index [HAQ-DI]:

This score is derived from self-report questionnaires designed to classify and assess functional capacity based on the patient's ability to do daily activities at home, work, or during leisure time. The eight sections are: clothing, arising, eating, walking, hygiene, reaching, gripping, and activities. Each segment has two or three questions. Scoring for each section ranges from 0 [no difficulty] to 3 [unable to perform]. In each section, the score assigned is the lowest score within that area. The sum of the eight scores from the eight parts is divided by eight [19].

Disease Activity Score 28 [DAS28]:

It contains streamlined assessments of 28 joints. DAS28 was determined to be practical for the assessment of rheumatoid arthritis disease activity in routine clinical practice [20]. DAS28 is a prevalent metric for assessing disease activity in rheumatoid arthritis [RA], offering patients a score that indicates the level of control over their condition and the efficacy of their therapy. DAS28 was computed utilizing a specialized calculator, predicated on the outcomes of various assessments, including joint evaluations [the count of tender and swollen joints], laboratory analyses [CRP and/or ESR], and the patient's subjective appraisal of their condition at the time of evaluation [visual analogue scale for pain and quality of life-disability index]. Generally, a lower DAS28 value indicates better management of rheumatoid arthritis, while a higher DAS28 score is frequently linked to increased joint destruction. Twenty-eight joints are assessed throughout the entire body. The joints were palpated, and the quantity of sensitive and swollen joints was enumerated.

Laboratory studies comprising: Routine assessments, Complete Blood Count [CBC], Hepatic function tests [SGPT, SGOT, Serum albumin, Bilirubin], Renal function assessments: [serum creatinine, blood urea nitrogen], Evaluation of ESR and CRP values, Evaluation of rheumatoid factor [RF] [21], anti-cyclic citrullinated peptide [anti-CCP] [22], and anti-mutated citrullinated vimentin [anti-MCV] levels [23], and Assessment of Rheumatoid Factor: by latex agglutination.

Statistical analysis:

The gathered data were systematically structured, tabulated, and subjected to statistical analysis utilizing the Statistical Package for the Social Sciences version 22 [IBM, SPSS Inc., USA]. Quantitative data were expressed as mean and standard deviation, whilst qualitative data were conveyed as relative frequency and percentage distribution. Group comparisons were conducted using one-way analysis of variance, independent samples t-test, Chi-square test, or Mann-Whitney U test. P values less than 0.05 were deemed significant.

RESULTS

In the present work, 50 subjects with rheumatoid arthritis were included; 40 of them [80.0%] were females and 10 [20.0%] were males with female to male ratio of 4:1; and there was no significant difference as regard to sex distribution between patients with Extra-articular manifestation [RA with ExRA group; group 1] when compared to those without Extra-articular manifestations [RA without ExRA group; group 2] as illustrated in table [1].

As regard to joint involvement, wrist joint was reported in 60.0%, PIP joint in 52.0%, MCP joint in 42.0%, Knee joint in 38%, hip joint in 32%, shoulder joint in 26%, elbow joint in 14% and ankle joint in 6.0%; and there was no significant difference between studied groups [Table 2].

As regard to extra-articular manifestations, it was in the form of sicca syndrome in 19 subjects, serositis in 15 subjects, rheumatoid nodules in 14 subjects, lung fibrosis in 4 subjects, neuropathy in 4 subjects and vasculitis in 2 patients as illustrated in table [3].

As regard to anti-CCP, it ranged from 4 to 530 IU/ml; and there was no significant increase in group 1 when compared to group 2. On the other hand, anti-MCV ranged from 8 to 500 IU/ml; and there was statistically significant increase of anti-MCV in group 1 when compared to group 2 [272.44±117.61 vs 91.08±125.71 respectively] as shown in table [4].

Regarding predictability of anti-CCP antibodies in diagnosis of extra-articular manifestations, the area under the curve was 0.72 denoting the lower predictability of this test, while the area under the curve was 0.85 for anti-MCV denoting better predictability with sensitivity of 96% and specificity of 76% at cut off point > 90 IU/ml [Table 5 and Figures 1 and 2].

Table [1]: Comparison between studied groups as regard to sex distribution

		Group				Total	
		RA with ExRA [n=25]		RA without ExRA [n=25]			
		n	%	n	%	n	%
Sex	Male	4	16.0%	6	24.0%	10	20.0%
	Female	21	84.0%	19	76.0%	40	80.0%
Statistics		X^2=0.50 , p =0.48					

Table [2]: Comparison between studied groups as regard to joint involvement

	RA With ExRA		RA without ExRA		Total		X2	p
	n	%	n	%	n	%		
Wrist joint	16	64.0%	14	56.0%	30	60.0%	0.33	0.56
PIP joint	12	48.0%	14	56.0%	26	52.0%	0.32	0.57
MCP joint	11	44.0%	10	40.0%	21	42.0%	0.08	0.77
Knee joint	9	36.0%	10	40.0%	19	38.0%	0.08	0.77
Hip joint	8	32.0%	8	32.0%	16	32.0%	0.01	1.0
Shoulder joint	6	24.0%	7	28.0%	13	26.0%	0.10	0.74
Elbow joint	4	16.0%	3	12.0%	7	14.0%	0.16	0.68
Ankle joint	1	4.0%	2	8.0%	3	6.0%	0.5	0.55

Table [3]: Extra-articular manifestations in the first group

	RA With ExRA	
	n	%
Sicca syndrome	19	76.0%
Serositis	15	60.0%
Rheumatoid nodules	14	56.0%
Lung fibrosis	4	16.05
Neuropathy	4	16.0%
Vasculitis	2	8.0%

Table [4]: Comparison between studied groups as regard to anti-CCP and anti-MCV antibodies

		Mean	S. D	Mini.	Maxi.	t	p
Anti-CCP	RA With ExRA	112.44	124.75	5.00	530.00	1.53	0.13
	RA without ExRA	62.64	104.00	4.00	420.00		
	Total	87.54	116.42	4.00	530.00		
Anti-MCV	RA With ExRA	272.44	117.61	20.00	500.00	***5.26***	***<0.001****
	RA without ExRA	91.08	125.71	8.00	360.00		
	Total	181.76	151.35	8.00	500.00		

Table [5]: Sensitivity and specificity of Anti-CCP and anti-MCV in prediction of extra-articular involvement in RA patients

	AUC	95% CI	Best cut off	Sensitivity	Specificity
Anti-CCP	0.72	0.60-0.84	>22	84.0%	72.0%
Anti-MCV	0.85	0.71-0.9	>90	96%	76%

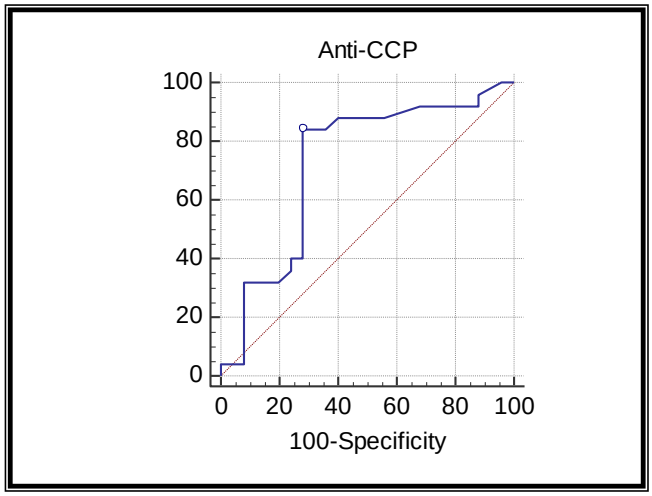

Figure [1]: ROC curve for diagnostic ability of anti-CCP

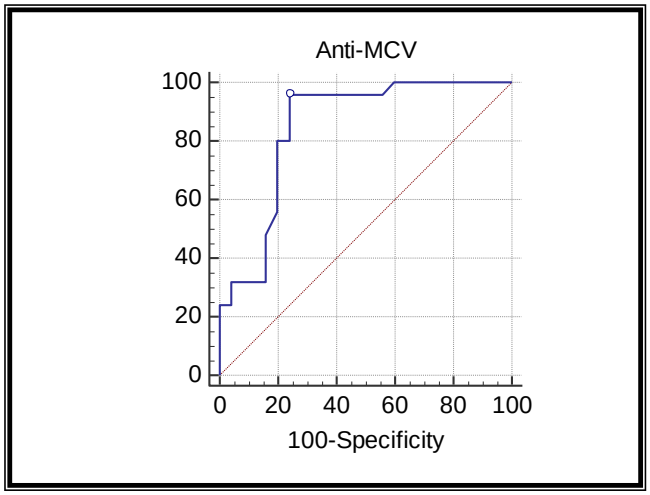

Figure [2]: ROC curve for diagnostic ability of anti-MCV

DISCUSSION

Rheumatoid arthritis [RA], which affects 0.8% of adults globally and more often women, causes joint inflammation and degradation, functional restrictions, working impairment, and a poor quality of life [24, 25]. Its cause is unknown, however biomarkers at different stages of this pathogenetically complex disease are being studied [26]. Biological indicators that aid early diagnosis of RA are important for disease management [27,28]. In everyday medicinal practice, autoantibodies are used to diagnose RA [29]. The American College of Rheumatology [ACR]/European League Against Rheumatism [EULAR] criteria for RA diagnosis now include serum RF and/or ACPA detection [17].

RF is still frequently employed as a biological marker, although its low RA specificity led to the faster development of ACPA. Anti-cyclic citrullinated peptide [anti-CCP] antibodies target synthetic peptides generated from human filaggrin [30]. Screening of dedicated peptide libraries has optimized CCP assays for anti-CCP antibody detection, and medical laboratories utilize the CCP2 and CCP3 ELISA tests [second and third generation]. Anti-Sa antibodies also give rise to ACPA members. RA synovial tissue contains citrullinated vimentin as the Sa antigen [31]. Anti-mutated citrullinated vimentin [anti-MCV] detects RA sensitively and specifically [23, 32].

Autoantibodies for early rheumatoid arthritis diagnosis. However, their efficacy in predicting extra-articular rheumatoid arthritis symptoms is unclear. Thus, this study examined the relationship between Anti-Cyclic Citrullinated Peptide and Anti-Mutated Citrullinated Vimentin positivity and extra-articular symptoms in rheumatoid arthritis patients.

In the present study, 40 of 50 rheumatoid arthritis patients [80.0%] were female and 10 [20.0%] were male, with a 4:1 female-to-male ratio. There was no significant difference between patients with extra-articular manifestations [RA with ExRA group; group 1] and those without. Similar results were discovered by **Turesson *et al.*** [11] who found female sex preponderance in their patients and no significant sex distribution difference between groups. Additionally, **Goeldner *et al.*** [33] found a 6.8:1 female/male RA ratio in their study. **Moura *et al.*** [34] found that 120 individuals had ExRA, 45.8% of RA patients in the study period, and 84.1% were female. Extra-articular symptoms included sicca syndrome in 19 individuals, serositis in 15, rheumatoid nodules in 14, lung fibrosis in 4, neuropathy in 4, and vasculitis in 2.

The following ExRAs have been reported in the literature: rheumatoid nodules; pericarditis; pericardial effusion; pleuritis; pleural effusion; interstitial pulmonary disease; pulmonary artery hypertension; Caplan's syndrome; Felty's syndrome; chronic disease anemia; thrombocytosis; neuropathy; scleritis; episcleritis; sicca syndrome; scleromalacia perforans and glomerulosis [35].

In this study, anti-CCP ranged from 4 to 530 IU/ml, and group 1 did not grow more than group 2. Although anti-MCV levels ranged from 8 to 500 IU/ml, there was a substantial increase in group 1 compared to group 2 [272.44±117.61 vs 91.08±125.71]. The area under the curve for anti-CCP antibodies in diagnosing extra-articular manifestations was 0.72, suggesting lower predictability, while anti-MCV had 0.85, indicating better predictability with 96% sensitivity and 76% specificity at cut off point > 90 IU/ml. Thus, in established rheumatoid arthritis, anti-MCV autoantibodies strongly correlated with extra-articular symptoms, while anti-CCP did not. These findings are similar to **Gonzalez-Lopez *et al.*** [14] who found no correlation between ExRA as a total group and anti-CCP positive. **Sghiri *et al.*** [16] found no correlation between ExRA and anti-CCP antibodies.

The present study contradicts **Salinas *et al.*** [36] who found a substantial correlation between anti-CCP and ExRA. However, **Turesson *et al.*** [11] found a link between anti-CCP and ExRA only in severe ExRA patients, not in general.

The present study contradicts **Gonzalez-Lopez *et al.*** [14] who found no connection between anti-MCV and ExRA as a complete group. Moreover, our data contradict **Sghiri *et al.*** [16]**. Nicaise Roland *et al.*** [37] have found that infliximab may lower anti-CCP and anti-MCV levels in RA patients.

We concur with **Rycke *et al.*** [38]**,** who reported no connection between anti-CCP and ExRA symptoms. Anti-CCP2 antibodies did not predict exRA in Turkish RA patients [13]. Greeks, like Northern Europeans, use anti-CCP2 antibodies to diagnose RA better than RF and correlate with radiographic joint deterioration [12]. Anti-MCV was also used to diagnose rheumatoid arthritis and predict ExRA symptoms. Diagnostic case–control studies on RA can use anti-MCV

instead of anti-CCP [39]. RA status and level were substantially linked with anti-MCV and anti-CCP [40]. A positive anti-MCV test raised radiographic progression probabilities by 7.3 against 5.7 for anti-CCP. improved anti-MCV levels improved progression probabilities. Anti-MCV IgG isotype antibodies can diagnose RA, especially in anti-CCP negative individuals [31, 37].

Additionally, anti-MCV antibodies had the greatest RA diagnosis specificity [97.5%] and sensitivity [86.6%] [41]. Anti-MCV autoantibodies had the highest AUC value [0.920] for RA patients compared to anti-CCP and RF antibodies. The area under a ROC curve [AUC] quantifies the test's ability to distinguish between those with and without the disease. Anti-MCV specificity and sensitivity for established RA were equivalent to **Ursum *et al.*** [42]**.** Anti-MCV sensitivity and specificity range from 49 to 74% to 79 to 96% in the literature[43]. Anti-MCV had higher sensitivity and unaltered specificity than anti-CCP in early RA patients compared to healthy controls [44]. Anti-MCV also outperforms anti-CCP in diagnosing poor radiographic prognosis in early RA patients. Serum anti-MCV levels can help diagnose RA, and anti-MCV and RF antibodies may be better predictive factors than RF and anti-CCP [45].

Disparities between studies can be attributed to differences in patient groups [46], early RA [47, 48] or established RA [23, 49], or number of cases studied [37].

Conclusion: Rheumatoid arthritis patients with anti-MCV antibodies exhibited strong extra-articular manifestation predictors. Anti-CCP is a powerful diagnostic marker of rheumatoid arthritis, especially in early stages, but it had no significant connection with extra-articular symptoms. The study's limited sample size limits it. Future large-scale studies must validate the results.

Conflict of interest: none

Financial Disclosure: None

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IJMA

INTERNATIONAL JOURNAL OF MEDICAL ARTS

VOLUME 6, ISSUE 11, November 2024

P- ISSN: 2636-4174
E- ISSN: 2682-3780