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Original Research Article

Prevalence of extraarticular manifestations in rheumatoid arthritis and their relationship with serological status and disease severity

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ABSTRACT

Background: Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that attacks the synovial joints. It affects body systems, such as the skin, cardiovascular, respiratory systems, and other systems, which manifest as extraarticular manifestations. This study aimed to correlate RA with extraarticular manifestations and its relationship with serological status.
Methods: One hundred fifty patients (30 male and 120 female) RA patients with a mean age of 49.9±11.9 attending the Rheumatology outpatient department and biological therapy center in Basrah Teaching Hospital were enrolled in the study and fulfilled the 2010 RA classification criteria of the American college of rheumatology/European league against rheumatism for RA. All the subjects underwent a thorough history, clinical examination, and laboratory investigations. Body mass index (BMI), the severity of pain using a visual analog scale (VAS) and disease activity using 28 joints (DAS28), and erythrocyte sedimentation rate were calculated for all patients. The relevant data were analyzed with appropriate statistical methods after 12 months.
Results: The mean age, age at onset, disease duration, and BMI were 49.9±11.9, 41±2.1, 14.6±5.8, and 26.8±4.8 respectively. The disease onset was acute in 45 (30%) and insidious in 105 (70%) patients. Anemia, rheumatoid nodule, sicca syndrome, Felty syndrome, Sjogren syndrome, and joint erosions were more frequent in seropositive than seronegative patients. There is no difference in joint deformities between seropositive and seronegative patients. DAS28, VAS, ESR, and CRP were higher in patients with extraarticular manifestations.
Conclusions: Extraarticular manifestations are significantly associated with seropositive disease and correlate to disease severity.

Keywords: Extraarticular manifestations, Rheumatoid arthritis, Rheumatoid factor, Seronegativity, Seropositivity

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory, autoimmune disease characterized by persistent joint inflammation that affects approximately 1-2% of the population worldwide and occurs mainly in females.[1] Although RA is primarily an articular disease, a series of extraarticular manifestations (ExRA) is still associated with the disease, such as ocular, pleuropulmonary, cardiovascular, renal, cutaneous, neurological system, and lymph node involvement. ExRA is a serious complication or outcome of long-term systemic inflammation associated with increased morbidity and mortality.[1] A population-based study confirmed that the presence of ExRA was the strongest predictor and was associated with high mortality in RA patients.[2] Nearly 40-50% of RA patients may suffer from some kind of ExRA at the onset of the disease or during the disease course and the morbidity varies based on different study designs and inclusion criteria.[3-5] The

etiology and pathogenesis of ExRA are currently still unclear. There are no reliable predictors for the development of ExRA, although many have been suggested.[6-8] They include such constitutional factors as male sex, association with HLA-related shared epitope genes, autoantibodies such as rheumatoid factor (RF), antinuclear antibodies (ANA), and anti-cyclic citrullinated peptide antibody (anti-CCP), as well as environmental factors such as smoking. [9-13] The innate and/or adaptive immune responses resulting from the interactions between the environmental and genetic factors yield chronic systemic inflammation that is characterized by the production of circulating immune complexes, low levels of complement protein C4, and higher amounts of CD4+, T and B lymphocyte.[14] Increased rheumatoid factor (RF) levels were observed in RA patients with ExRA, suggesting that RF may be implicated in the formation of CICs that leads to the maintenance of systemic inflammation.[15] Even though the prognosis of RA is improving with the improvement in the management of the disease; but, it is obvious that some medications have a negative impact on the occurrence of ExRA. Some case reports showed a reduced incidence of severe ExRA in RA patients treated with methotrexate (MTX) and cyclophosphamide, a high-dose corticosteroid; however, the impact of anti-tumour necrosis factor (TNF) on ExRA is still under debate.[1,16]. Due to the systemic inflammatory process, the incidence of mortality in RA is increased by four-fold compared with the general population.[17] Based on the background of ExRA in RA, we suggested that serological, laboratory parameters and severity of the disease may be correlated to the ExRA. In this study, we aimed to declare the association between ExRA and the serological status of RA patients.

METHODS

This was a cross-sectional retrospective study that included 150 (30 male and 120 female) RA patients. They were previously diagnosed with RA according to the 2010 American college of rheumatology/European league against rheumatism diagnostic criteria.[18] The patients were selected from the rheumatology outpatient clinic and biological therapy center in Basrah teaching hospital from January 2021 to August 2022. The demographic profiles of the patients, as well as the disease duration, age at initial presentation, and presence of extraarticular manifestations, were evaluated based on their medical records. Family history was considered positive if at least one first-degree relative had been diagnosed with RA. Laboratory blood tests, including erythrocyte sedimentation rate (ESR), C reactive protein (CRP), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (Anti-CCP) levels, were performed routinely at admission to the clinic. Radiological changes were detected on radiography by both rheumatologists and radiologists. Extraarticular symptoms were described as follows: anemia (hemoglobin <11 g/dl), rheumatoid nodules were described as the presence of subcutaneous nodules >5 mm on extensor surfaces of extremities, carpal tunnel syndrome was the presence of subjective complaints in combination with NCV findings, sicca symptoms were the presence of dry mouth and eyes, Raynauds phenomenon was the presence of cold extremities on exposure to cold or stress, pulmonary involvement was the presence of pleuritis, interstitial changes. Felty syndrome was the presence of leucopenia and splenomegaly not attributable to another reason. Normal ranges of laboratory parameters were described as follows: CRP (normal 0-5), ESR (normal 20 mm/h by Westergren method), RF (normal <5 by nephelometry method), anti-CCP (normal <20 by ELISA method). Body mass index (BMI), the severity of pain using a visual analog scale (VAS) and disease activity using 28 joints (DAS28), and ESR were calculated for all patients.[19] Patients less than 18 years of age, and patients with other autoimmune, diabetes mellitus, congestive heart failure, and chronic liver disease were excluded from the study. Informed written consent was obtained from all participants prior to their involvement. It was performed in accordance with the standards of the Declaration of Helsinki.

Statistical analysis

SPSS Software version 25.0 was used for data analysis. Percentages and mean were used to present the data in tables. A comparison of study groups was carried out using the Chi-square test for categorical data and Student's t-test for continuous data, p value of <0.05 was considered statistically significant.

RESULTS

Of the 150 RA patients, there were 30 (20%) men and 120 (80%) women, and the ratio of men to women was 1: 4. The mean age, age at onset, disease duration, and BMI were 49.9±11.9, 41±2.1, 14.6±5.8, and 26.8±4.8 respectively. The disease onset was acute in 45 (30%) and insidious in 105 (70%) patients. 18 (12%) and 32 (21.33%) were smokers and had a family history of RA, respectively. The overall extraarticular manifestations were 66.66%, as shown in (Table 1). Anemia, rheumatoid nodule, thrombocytosis, sicca syndrome, Felty syndrome, and Sjogren syndrome were more frequent in seropositive than seronegative patients; the difference was statistically significant, p values were 0.012, 0.022, 0.022, and <0.05 respectively. There were no statistically significant differences in the occurrence of the Raynauds phenomenon, lung involvement, and carpal tunnel syndrome between the two groups (p>0.05 for all), as shown in (Table 2). Apart from joint erosion, which is more frequent in seropositive patients (p=0.043), ulnar deviation, swan neck deformity, Z deformity, and Boutonniere deformity were equally affected by both seropositive and seronegative RA patients (p>0.05 for all) as shown in (Table 3). Higher DAS28, VAS, and inflammatory markers were observed in seropositive than seronegative RA patients; the differences were

statistically significant, and the P values were 0.033, 0.022, 0.024, and 0.022, respectively as shown in (Table 4).

Table 1: Demographic distributions and disease characteristics of patients with rheumatoid arthritis.

Characteristics	N (%)
Total	150 (100)
Males	30 (20)
Females	120 (80)
Mean age ±SD (years)	49.9±11.9
Age groups(years)	
20-39	25 (16.67)
40-59	95 (63.33)
≥60	30 (20)
The mean age of onset±SD (years) for men	45±2.3
The mean age of onset±SD (years) for women	38±3.1
Disease onset	
Acute	45 (30)
Insidious	105 (70)
Mean disease duration±SD (years)	14.6±5.8
Body mass index (mean ±SD)	26.8±4.8
Extra-articular manifestations	100 (66.66)
Smoking	18 (12)
Family history	32 (21.33)
Medications	
Methotrexate	140 (93.33)
Antimalarial	86 (57.4)
Sulfasalazine	78 (52)
Leflunomide	11 (7.33)
Prednisolon	40 (26.66)
Etanercept	80 (53.33)
Remicade	30 (20)
Humera	14 (9.33)
Remsima	2 (1.33)
Rituximab	2 (1.33)

DISCUSSION

RA is a chronic multisystem disabling disease with various extra-articular manifestations frequently leading to physical and psychological consequences with a considerable socioeconomic burden.[20] In this study, the prevalence of ExRA was 66.66% among our study sample. This is similar to the prevalence of ExRA in the British population which is 68%, but higher than in North American populations (40%).[21-25] Based on our search of the literature, no previous study has evaluated the prevalence of ExRA in Iraq. In this study, the mean age at the onset of RA was 41.5±2.2 years, which is similar to other studies.[15,20] In our study, it was found that females had a relatively earlier onset of the disease as compared to males, which was in accordance with a study done in Pakistan by van der Woude et al.[13] Females had highly affected by RA than males in this study, which was in accordance with other studies.[26,27] We found that 70% of patients had an insidious onset. In this study, 81.33% of the patients were seropositive, similar to numerous studies.[26,28-30] ExRA patients have significantly high titer and positivity of RF and Anti-CCP, and they found (67.2%) ExRA patients have positive Anti-CCP.[31] However, another study postulated that Anti-CCP levels tended to be higher in patients with ExRA, but this was not statistically significant.[32] Anemia was the most common ExRA in our study population, occurring in 42.62% of patients, while rheumatoid nodules were found in 22.95% of patients, thrombocytosis occurred in 17.21%, followed by sicca, Sjogren, and Felty syndrome in percentages of 12.3%, 9.83%, and 9.01% respectively. All these ExRA were more prevalent in seropositive RA patients than seronegative RA patients. These findings were very similar to those found in other studies.[26,27,33] In our study, the percentage of different types of joint deformities does not differ in seropositive than in seronegative patients.

Table 2: Extra-articular features in both seropositive and seronegative patients with rheumatoid arthritis.

Mean feature	Seropositive RA N (%)	Seronegative RA N (%)	P value
Total	122 (81.33)	28 (18.67)	-
Anaemia	52 (42.62)	5 (17.85)	0.012
Rheumatoid nodule	28 (22.95)	2 (7.14)	0.022
thrombocytosis	21 (17.21)	2 (7.14)	0.042
Sicca syndrome	15 (12.3)	1 (5.55)	0.022
Raynauds phenomenon	6 (4.91)	1 (5.55)	>0.05
Lung involvement	14 (11.47)	2 (11.11)	>0.05
pericarditis	5 (4.09)	1 (5.55)	>0.05
Felty syndrome	11 (9.01)	1 (5.55)	<0.05
Sjogren	12 (9.83)	1 (5.55)	<0.05

CTS: Carpal tunnel syndrome

While joint erosion and destruction were more frequent in seropositive than in seronegative patients. Numerous factors were importantly associated with joint destruction evaluated by Larsen grade and Sharp/Van Der Heijde method (SHS), but the anti-CCP serological status was particularly associated with the destruction of the wrist joint rather than the feet, while RF serological status was

not associated with the destruction of either the wrists or the feet.[34]

Table 3: Frequency of joint deformities and erosion in both seropositive and seronegative patients with rheumatoid arthritis.

Joint deformity	Seropositive RA N (%)	Seronegative RA N (%)	P value
Total	122 (81.33)	28 (18.67)	-
Ulnar deviation	35 (28.68)	5 (27.77)	>0.05
Swan neck	32 (26.22)	5 (27.27)	>0.05
Z deformity	32 (26.22)	4 (22.22)	>0.05
Boutonniere	23 (18. 85)	3 (16.66)	>0.05
Joint erosion	39 (31.96)	2 (11.11)	0.043

Table 4: differences in disease activity, pain severity, and inflammatory markers in both seropositive and seronegative patients with rheumatoid arthritis.

Parameter	RA patients with extra-articular manifestations	RA patients without extra-articular manifestations	P value
Total N (%)	57 (38)	93 (62)	-
DAS 28	4.6	2.2	0.033
VAS	7	3	0.022
ESR	38	14	0.024
CRP	6	2	0.022

DAS 28: disease activity score using 28 joints, VAS: visual analog scale, ESR: erythrocyte sedimentation rate, CRP: C reactive protein.

Previously many indicators were reported to predict the destruction of joints, including female sex, IL-6, MMP-3, low bone density, biomarkers of cartilage and bone, and the first-year progression.[35- 38]

Recently reported a crucial contribution of DRB1 in association with joint destruction.[39] Among these, anti-CCP and RA status are the most frequently discussed and analyzed predictors of joint destruction and/or remission.[36,40] We found all disease activity indices and inflammatory markers were higher in seropositive than those in seronegative patients.

One of the limitations of this study is the study sample size and the second limitation is that the studied patients are already on treatment which may interfere with the presence of the ExRA.

CONCLUSION

Extra-articular manifestations are present in a substantial number of RA patients, which is often overlooked or missed by the physician. Extra-articular manifestations are associated with more severe disease. Seropositivity also has a positive relationship with extra-articular manifestations and the presence of both usually indicates more severe disease.

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