ORIGINAL

Extra-articular manifestations in rheumatoid arthritis and its relationship with serology markers in Saudi patients

Identificación de los factores que afectan la atención integral de las personas mayores en Irán

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Abstract

Introduction: Extra-articular manifestations of Rheumatoid arthritis (ExRA) are defined as all the diseases and symptoms which are not directly linked to the musculoskeletal system and can occur at any age after onset. The study aimed to investigate the frequency of ExRA patients and to assess its relationship to serology markers.

Methods: This observational cross-sectional study was carried out on 60 Saudi patients with newly or previously diagnosed RA according to 2010 American College of Rheumatology-European League against Rheumatism criteria. They were followed in the Rheumatology Clinic at King Khalid Majmaah Hospital (KKMH) from January 2017 to December 2020. Data collected was analyzed by SPSS 26 and appropriate statistical tests were applied.

Results: A total of sixty patients (52 women; 8 men) who visited KKMH were included in this study. The mean age of the patients was 47.87 ± 11.55 years, and the female-to-male ratio was 6.5:1. Out of the total, 14 patients (23.3%) had a family history of RA. 18 patients developed ExRA features; anemia occurred in 30%, Sjögren's syndrome in 8.3%, thrombocytosis in 6.7%, and leukopenia in 3.3%. Further, 40 patients (66.7%) were positive for RF, 47 (78.3%) for anti-CCP antibodies, and both markers were positive in 36 (60%) of the patients. Among 18 patients with ExRA, the percentage of positive RF and anti-CCP were 25% and 32%, respectively, while 42 patients with no ExRA, both markers were positive in 75 % and 68 %, respectively.

Conclusion: Anemia is the most common extra-articular manifestation of TA, however, no significant relationship was observed between serology markers and extra-articular manifestations of RA.

Keywords: Rheumatoid arthritis, extra-articular manifestations, serology markers, Saudi patients.

Resumen

Introducción: Las manifestaciones extra articulares de la artritis reumatoide (ExRA) se definen como todas las enfermedades y síntomas que pueden relacionarse directamente con el sistema musculoesquelético y que pueden aparecer a cualquier edad tras su inicio. El estudio tuvo como objetivo investigar la frecuencia de los pacientes con ExRA y evaluar su relación con los marcadores serológicos.

Métodos: Este estudio observacional transversal se llevó a cabo en 60 pacientes saudíes con AR recién diagnosticada o previamente diagnosticada según los criterios del American College of Rheumatology-Liga Europea contra el Reumatismo de 2010. Fueron seguidos en la Clínica de Reumatología del Hospital King Khalid Majmaah (KKMH) desde enero de 2017 hasta diciembre de 2020. Los datos recogidos se analizaron con SPSS 25 y se aplicaron las pruebas estadísticas adecuadas.

Resultados: Un total de sesenta pacientes (52 mujeres; 8 hombres) que visitaron el KKMH fueron incluidos en este estudio. La edad media de los pacientes era de 47,87 ± 11,55 años, y la proporción entre mujeres y hombres era de 6,5:1. Del total, 14 pacientes tenían antecedentes familiares de AR. 18 pacientes desarrollaron rasgos ExRA; la anemia se presentó en el 30%, el síndrome de Sjögren en el 8,3%, la trombocitosis en el 6,7% y la leucopenia en el 3,3%. Además, 40 pacientes fueron positivos para el FR, 47 para los anticuerpos anti-CCP, y ambos marcadores fueron positivos en 36 de los pacientes. Entre los 18 pacientes con ExRA, el porcentaje de RF y anti-CCP positivos fue del 25% y el 32%, respectivamente, mientras que en 42 pacientes sin ExRA, ambos marcadores fueron positivos en el 75% y el 68%, respectivamente.

Conclusiones: La anemia es la manifestación extra articular más frecuente de la AT, sin embargo, no se observó una relación significativa entre los marcadores serológicos y las manifestaciones extra articulares de la AR.

Palabras clave: Artritis reumatoide, manifestaciones extra articulares, marcadores serológicos.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune condition characterized by inflammatory polyarthritis that is recurring and progressive, leads to tenosynovitis, erosion, destruction of the joint surface, and deformity[1]. RA affects 1-2% of the world's population and occurs two to three times more frequently in women than in men[2]. Extra-articular manifestations of RA (ExRA), defined as all the diseases and symptoms which are not directly linked to the musculoskeletal system[3]. ExRA can occur at any age after onset, and it is more common in men than women[4]. Several studies have reported an ExRA with a frequency ranging from 18% to 41%, reasons for the wide range due to study design and differences in the enrolled population[5]. Although there are no reliable predictors for the development of ExRA, some scientific reviews have reported that risk factors could be associated with it, such as male gender, smoking, and positive serology markers (RF, CCP and ANA) and HLA-region gene[6]. Many of these ExRA are related to the more active and severe RA, so it is considered a severe condition and emphasized the role of ExRA as predictors of premature mortality in patients with RA[7]. ExRA patients should be monitored and treated aggressively[8].

In this study, we reviewed the incidence and frequency of ExRA among RA patients from the Majmaah province population attended at the rheumatology clinic in King Khalid Majmaah Hospital (KKMH), Saudi Arabia (SA), and identified the relationship between serology markers and ExRA.

Materials and methods

This is a cross-sectional retrospective study involving 60 RA patients from Saudi Arabia. They were newly or previously diagnosed with RA according to the 2010American College of Rheumatology/European League Against Rheumatism Diagnostic Criteria[9]. The patients were selected from the rheumatology clinic in KKMH from January 2017 to December 2020. The research was approved by the central institutional review board of the Ministry of Health, SA.

The demographic profiles of the patients, as well as the length of the disease at the time of the initial presentation (classified as Less than 5 years, Between 5 to 10 years, and more than 10 years), and presence of extra-articular manifestations of RA (ExRA) 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 rheumatoid factor (RF) and anti-cyclic citrullinated peptide (Anti-CCP) levels, were performed routinely at admission to the clinic.

Extra-articular manifestations of RA included Sjogren syndrome, which was defined by xerophthalmia and xerostomia. Hematological changes included leucopenia (WBC count <4×K/ul), thrombocytosis (platelet count > 400 K/ul)) and anemia (normochromic or hypochromic). During the study, the relationship between serology markers and extra-articular manifestations was assessed. All characteristic features of patients with RA seen at KKMH were statistically analyzed using IBM SPSS version 26 (IBM Corp., Armonk, NY, USA). Age was defined as mean and SD, whereas categorical data was expressed as frequencies and percentages. Pearson's chi-square and Fisher's exact tests were used to test for associations between study variables. A p-value of 0.05 was considered important.

Results

Clinical characteristics of the RA patients

This research included a total of sixty patients (52 women, 86.7 percent; 8 men, 13.3 percent) who visited KKMH. The patients' average age was 47.87 11.55 years, with a female-to-male ratio of 6.5:1. The duration of the disease at the time of the study for most of the patients was Less than 5 years, 36 subjects (60%), followed by Between 5 to 10 years, 13 subjects (21.7%), and more than 10 years, 11 subjects (18.3%). Out of the total, 14 patients (23.3%) had a family history of RA. In our study, extra-articular manifestations were found in 18 patients (30%). Further, 40 (66.7%) patients were positive for RF, 47 (78.3%) for anti-CCP antibodies, and both markers were positive in 36 (60%) of the patients. **Table I** illustrates the clinical characteristics of the RA patients.

Table I: Characteristics features of rheumatoid arthritis population (n=60).

Parameter	n (%)
Mean age (years)	47.87 ± 11.55
Gender	
Female	52 (86.7)
Male	8 (13.3)
Female: Male ratio	
Duration of the disease (years)	
Less than 5	36 (60.0)
Between 5 - 10	13(21.7)
More than 10	46 (76.7)
Family history of RA	
No	46 (76.7)
Yes	14 (23.3)
Extra-articular manifestation	
No	42(70)
Yes	18(30)
Rheumatoid factor (RF)	
Positive	40 (66.7)
Negative	20 (33.3)
Anti-cyclic citrullinated peptide (Anti-CCP)	
Positive	47(78.3)
Negative	13(21.7)
Rheumatoid factor (RF) **and Anti-cyclic citrullinated peptide (Anti-CCP)**	
Positive	36 (60.0)
Negative	9 (15.0)

Main extra-articular features

The main extra-articular features are shown in **table II**. Anemia was found in 18 patients (30%). Normochromic normocytic and hypochromic microcytic were the commonest, affecting 7 (11.7%) anemic patients, while hypochromic normocytic anemia affects only four (6.7%) patients. Sjogren syndrome and thrombocytosis were present in 5 (8.3%) and 4 (6.7%) patients. Leukopenia was the least frequent feature found in RA patients, occurring in 2 patients only (3.3%).

Relationship between RF, Anti-CCP, and extra-articular manifestation in RA patients

The relationship between RF, Anti-CCP, and extra-articular manifestation in RA patients is shown in **table III**. The percentage of positive RF and anti-CCP in 18 patients with ExRA, were (25%) and (32%), respectively, while in

42 patients with no ExRA, both markers were positive in (75 %) and (68 %), respectively. We did not report any statistically significant between the status of serology markers in the two RA groups (with and without ExRA).

Discussion

This study aimed to investigate the extra-articular manifestations in rheumatoid arthritis and its relationship with serology markers among about 60 Saudi patients attending the rheumatology clinic at KKMH. Based on our search of the literature, no previous study has evaluated the ExRA in the Majmaah province, SA. The mean age of patients in the RA group was 47.87 ± 11.55 years, and the majority, 52 (86.7%), were female (female-to-male ratio, 6.5:1). These findings are consistent with previously published reports[10,11]. The duration of the disease at the time of the first presentation for the majority of the patients was Less than 5 years (60%) and higher than that observed in the Al-Ghamdi study[12].

Family history considers as one of the strongest risk factors for developing RA and may predict the disease course. It is an integral part of the workup and diagnosis of RA. In the present review, fourteen patients reported at least one first-degree relative affected by RA, higher than the proportion reported by Al-Herz[13].

Table II: Main extra-articular manifestations of rheumatoid arthritis population (n=60).

Extra-articular manifestations	n (%)
Sjogren syndrome	5 (8.3)
Anemia	18 (30.0)
Normochromic normocytic	7 (11.7)
Hypochromic normocytic	4 (6.7)
Hypochromic microcytic	7 (11.7)
Leukopenia	2 (3.3)
Thrombocytosis	4 (6.7)

Table III: Determine the association between the RF, Anti-CCP and extra-articular manifestation in RA patients.

Associations							
Items	Overall n=60 (%)	RF −20 (33.3)	RF +40 (66.7)	p-value	Anti-CCP - 13(21.7)	Anti-CCP + 47(78.3)	p-value
Extra-articular manifestation							
No	42(70)	12(60)	30 (75)	0.231	10 (77)	32 (68)	0.538
Yes	(30)18	8 (40)	10 (25)		3 (23)	15 (32)	
Sjogren syndrome							
No	55 (91.7)	19 (95)	36 (90)	0.508	13 (100)	42(89.4)	0.219
Yes	5 (8.3)	1 (5)	4 (10)		0 (0)	5 (10.6)	
Anemia							
No	42 (70.0)	15 (75)	17(67.5)	0.185	11(84.6)	31(66)	0.943
Yes	18 (30.0)	5 (25)	13(32.5)		2 (15.4)	16 (34)	
Normochromic Normocytic							
No	53 (88.3)	17(85)	36 (90)	0.569	12(92.3)	41(87.3)	0.614
Yes	7 (11.7)	3 (15)	4 (10)		1(7.7)	6 (12.7)	
Normocytic Hypochromic							
No	56 (93.3)	19 (95)	37(92.5)	0.714	13 (100)	43 (91.5)	0.276
Yes	4 (6.7)	1 (5)	3 (7.5)		0 (0)	4 (8.5)	
Microcytic Hypochromic							
No	53 (88.3)	19 (95)	34 (85)	0.255	12(92.3)	41(87.3)	0.614
Yes	7 (11.7)	1 (5)	6(15)		1(7.7)	6 (12.7)	
Leukopenia							
No	58(96.7)	19 (95)	39(97.5)	0.611	13 (100)	45(95.7)	0.449
Yes	2 (3.3)	1 (5)	1 (2.5)		0 (0)	2 (4.3)	
Thrombocytosis							
No	56 (93.3)	19 (95)	37(92.5)	0.714	12(92.3)	44 (93.6)	0.866
Yes	4 (6.7)	1 (5)	3 (7.5)		1(7.7)	3 (6.4)	

At present, biomarkers such as RF and Anti-CCP have important diagnostic value for RA. Several studies prove that Anti-CCP is a more specific marker than RF due to their high specificity to RA. Our cross-study showed patients positive for RF, anti-CCP and both of them were (66.7%), (78.3%) and (60%), respectively. These results are comparable to the proportion reported by other studies[14-15].

Extra-articular can involve many systems and organs such as the skin, cardiopulmonary, hematology, nervous, eyes, gastrointestinal and renal, and It is significantly present more frequent in seropositive patients[16]. However, there is no agreed classification for these manifestations due to the variation in definitions and criteria observed in different study designs. In our study, the frequency of ExRA was 30% among our patients. However, these results disagreed with previous investigations[12].

In scientific reviews, the main ExRA has been evaluated. The hematological abnormalities of ExRA are broad and include anemia, leukopenia, thrombocytopenia, thrombocytosis, and malignancies, and could present either at the time of diagnosis or during the course of the disease[17]. Anemia is one of the most common ExRA symptoms, and it can be caused by a number of factors including disease activity, medication side effects, dietary deficiencies, and gastrointestinal bleeding[18] Anemia was the most common ExRA in our population, occurring in 18 (30.0%) of patients, with normochromic normocytic and hypochromic microcytic were much higher among our patients (11.7%), followed by hypochromic normocytic found in 4 (6.7%) of patients. These findings are consistent with those of Cojocaru et al.[4]. The percentage of thrombocytosis was (6.7%) among our patients, while leukopenia occurred in (3.3%), and these findings were less than the reported data by Al-Ghamdi[12].

Keratoconjunctivitis sicca is, by far, the most common ocular manifestation in individuals with RA[19], and it is described as an aqueous tear deficiency. The incidence of keratoconjunctivitis sicca is between 11.6% to 50%[20], and it is frequently observed together with xerostomia in a secondary Sjögren's syndrome[19]. This disorder needs artificial tears for a lifetime 21. In our study, Sjögren's syndrome was found in 8.3% of patients, and it is comparable to that reported in the Al-Ghamdi study 6%[12]. **Table II** presents the details of the main ExRA found in this study.

Table III presents the details of the association between the RF, Anti-CCP, and ExRA patients found in this study. Many studies have examined the relationship between them, such as Turesson et al., suggested that both serology markers (Anti-CCP and RF) were associated with severe ExRA[22]. Also, Kim study found that Anti-CCP levels are significantly high in patients with ExRA[23]. Moreover, the results of the Egypt study showed that

ExRA patients have significantly high titer and positivity of RF and Anti-CCP, and they found (67.2%) ExRA patients have positive Anti-CCP[24]. However, another study postulated that Anti-CCP levels tended to be higher in patients with ExRA, but this was not statistically significant[22].

In our study, among 18 patients with ExRA, the percentage of positive RF and anti-CCP were (25%) and (32%), respectively, while 42 patients with no ExRA, the percentage of positive RF and anti-CCP were (75%) and (68%), respectively. We compared the status of RF and anti-CCP in the two RA groups (with and without the main ExRA), and we did not observe any statistical significance. These results are inconsistent with previously published reports[22-24].

Overall, ExRA can involve multiple organs that cause comorbidities and may also have psychological and social consequences. ExRA has an association with RA disease activity; therefore, it has had a role as a predictor of early mortality among RA patients. Based on our findings, the incidence and frequency of ExRA among studied groups are comparable to the proportion reported by others. On the other hand, the serology markers were not prevalent in the presence or absence of ExRA among RA. However, in future studies, the number of investigated patients must be increased to confirm our findings and to accurately represent the entire population.

Conclusion

Anemia is the most common extra-articular manifestations of RA and present in up to one-third of the studied group. However, our data did not observe any relationship between serology markers and extra-articular manifestations of RA. More extensive sample size studies are needed in the future to confirm our findings.

Acknowledgments

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