



EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

Medicine

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ABSTRACT

Introduction: Despite the predominant osteoarticular and periarticular manifestations, Rheumatoid Arthritis (RA) is a systemic disease, often associated with extra-articular manifestations. The present study was aimed to assess extra-articular manifestations among patients who were diagnosed with RA and to also assess patient related factors associated with the presence of extra-articular manifestations.

Methodology: We included 50 patients with RA, with a disease duration of more than 5 years and those who took at least 3-year treatment with disease modifying agents. Extra-articular complications were diagnosed clinically and laboratory confirmation was done as deemed necessary by the treating physician. Disease characteristics including deformities or other morbidities and associated complications were recorded.

Results: Of the 50 patients included in the study, mean age of the patients was 53.4 years and 14 patients (28%) had any kind of extra-articular manifestation. The most common extra-articular manifestation was Secondary Sjogren's Syndrome (22%), osteoporosis (18%) and interstitial lung disease (15.5%). Less common extra-articular manifestations were nodules (12%), fibromyalgia (10%), coronary artery disease (8%), peripheral neuropathy (6%), vasculitis (3%), eye manifestations (2%), malignancy (1%) and amyloidosis (1%). Increasing age, disease duration and severity as assessed by Disease Activity Score were found to be significantly associated with the presence of extra-articular manifestation.

Conclusions: Our study found that extra-articular manifestations among RA patients were found to have a significant association with many patient-related variables like age, disease duration and disease severity.

KEYWORDS

INTRODUCTION

The prevalence of chronic diseases in developing countries like India is rising and among these, rheumatoid arthritis (RA) stands out as a major cause of high morbidity. RA is an autoimmune disorder with a worldwide prevalence of 1-2% and women have been shown to be affected two to three times more commonly than men. Malaviya et al reported a prevalence of 0.7% in Haryana and a prevalence of 5.2% of rheumatoid symptoms were found among patients from West Bengal by Kar et al. When RA is left uncontrolled, the RA patient may experience joint deterioration, severe disability, decreased quality of life, the onset of comorbidities and premature mortality. A better control of disease activity in the last decades due to the availability of more efficacious drugs and novel treatment strategies have resulted in a lower frequency of extra-articular manifestations of RA, as well as better outcomes in many patients. Despite its predominant osteoarticular and periarticular manifestations, RA is a systemic disease, often associated with extra-articular manifestations. The reported incidence of extra-articular manifestations varies among studies and geographical settings. Part of this variation is due to the fact that reporting has been inconsistent, as some investigators have considered all possible manifestations, whereas others focused only on severe ones. Also, many of the study have reported data of patients either admitted in the hospital or those visiting the outpatient clinic, thereby reporting a higher incidence as compared to those study which were conducted in the community. The present study was aimed to assess extra-articular manifestations among patients who were diagnosed with RA and to also assess patient related factors associated with the presence of extra-articular manifestations.

METHODOLOGY

Study Design and Sampling

This cross-sectional study was conducted in the Department of Medicine, DY Patil School of Medicine, Navi Mumbai. Patients diagnosed with RA (classified as per 1987 ACR criteria) and presented to our department from July 2019 till December 2019 were included in the study to assess extra-articular complications. We included 50 patients with RA diagnosed as per 1987 ACR criteria, with a disease duration of more than 5 years and those who took at least 3 years treatment with DMARDs. We excluded patients aged < 18 years or those with with Overlap syndrome. The patients were explained the purpose of the study and a written consent was obtained from them. The study was approved by the Institutional Ethics Committee. Precautions were taken to ensure confidentiality. Data collection forms did not reveal name and ID of the patients included in the study.

Data Collection and Data Analysis

The patients were classified as per the revised ACR 1987 guidelines for

Rheumatoid Arthritis. These patients were subjected to various predefined tests after obtaining their consent. Demographic profile, clinical features, laboratory data, treatment details were noted. Disease characteristics including deformities or other morbidities and associated complications were recorded. Using a pre-defined semi-structured study proforma, we noted the demographic profile, medical history, systemic activity of RA using Disease Activity Score (DAS28) and laboratory parameters including inflammatory markers, rheumatoid factor and anti-cyclic citrullinated peptide status. Extra-articular complications were diagnosed clinically and laboratory confirmation was done as deemed necessary by the treating physician. Descriptive analysis of quantitative parameters was expressed as means and standard deviation and that of ordinal data were expressed as absolute number and percentage. Cross tables were generated and chi square test was used for testing of associations, p-value < 0.05 was considered statistically significant. All analysis were done using SPSS software, version 24.0.

RESULTS

Of the 50 patients included in the study, mean age of the patients was 53.4 years, 44% were aged between 50 to 70 years. Females comprised 78% of the total study population (Table 1). Mean duration of RA in our study population was 12.67 years and 62% had their disease duration 15 years or less. The common comorbidity observed in our patients population was hypertension (22%), coronary artery disease (14%) and diabetes mellitus (12%). Serology examination revealed 88% were positive for Rheumatoid Factor, 76% were positive for anti-cyclic citrullinated peptide (anti-CCP) and 54% tested positive for anti-neutrophilic antibody. Disease severity assessed using DAS28 revealed that 22% had a mild disease, 26% had moderate disease and 52% had a severe disease. In our study 14 patients (28%) had any kind of extra-articular manifestation (Table 2). The most common extra-articular manifestation was Secondary Sjogren's Syndrome (22%), osteoporosis (18%) and interstitial lung disease (15.5%). Less common extra-articular manifestations were nodules (12%), fibromyalgia (10%), coronary artery disease (8%), peripheral neuropathy (6%), vasculitis (3%), eye manifestations (2%), malignancy (1%) and amyloidosis (1%). Table 3 describes how presence of any extra-articular manifestation is associated with patient related variables. Increasing age was found to be significantly associated with the presence of extra-articular manifestation, as all 7 patients aged more than 70 years had an extra-articular manifestation of RA (p value < 0.01). Gender was associated with the presence of an extra-articular manifestation (p value = 0.48). Of the 19 patients with disease duration more than 15 years, 12 (63%) had an extra-articular manifestation and thus increasing disease duration was associated with the presence of an extra-articular manifestation (p value < 0.01).

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Increasing severity was also found to be significantly associated with the presence of an extra-articular manifestation, as 12 of the 26 patients (46%) with severe disease were found to have an extra-articular manifestation (p value < 0.01).

DISCUSSION

The present study was conducted in our department to know the incidence of extra-articular manifestations among patients diagnosed with RA, with at least 5 years of duration and taking at least 3 years DMARDs. Of the 50 patients included in the study, mean age of the patients was 53.4 years, 44% were aged between 50 to 70 years. Women have been shown to be affected two to three times more often than men and the peak onset is between the ages of 50 and 75 years. We observed that increasing age was found to be significantly associated with the presence of extra-articular manifestation, as all 7 patients aged more than 70 years had an extra-articular manifestation of RA. Also, females comprised 78% of our total study population. Hochberg and colleagues performed a retrospective analysis of 16,752 patients with incident RA, with mean age being 59.8 ($\pm$ 13.5) years, mostly (72%) females. Haroon et al included 136 patients of RA with the mean duration of RA of 9 $\pm$ 5.8 years and the mean age of the patients were 44.4 $\pm$ 10.5 years.

In our study, the most common extra-articular manifestation was Secondary Sjogren's Syndrome (22%), osteoporosis (18%) and interstitial lung disease (15.5%). Out of a total of 609 patients, Turesson et al reported the most common extra-articular manifestations to be rheumatoid nodules (n=172, 28%), secondary Sjogren's syndrome (n=58, 9.5%), and pulmonary fibrosis (n=34, 5.5%). Haroon et al reported secondary Sjogren's syndrome (n=17), subcutaneous nodules (n=10) and interstitial lung disease (n=7) to be the most common extra-articular manifestations.⁸ Myasoedova et al included 463 RA patients, of which 184 patients developed an incident extra-articular manifestation during the follow-up, and reported that the most common manifestation were subcutaneous nodules, keratoconjunctivitis sicca, and Sjogren's syndrome. In a systematic review, Handa et al commented that data on comorbidities and extra-articular manifestations were not commonly reported, and few similarities were found as to the type and number collected across studies. Higher frequencies of extra-articular manifestations have been reported in northern European countries than in southern countries, suggesting that environmental and genetic factors play a role in the pathogenesis of these complications.

There are a few limitations of this study. First, ours is a cross sectional study, so causality of the extra-articular manifestations cannot be ascertained from this dataset. It is also possible that some of the extra-articular manifestations were not diagnosed. Then, we did not note the duration and severity of the extra-articular manifestations. Third, many patients from the pre-biological era were included in the study, which can lead to a selection bias.

CONCLUSION

Our study assessed extra-articular manifestations among RA patients with at least 5 years of duration and found that 28% of all patients had one or more extra-articular manifestations. These complications were also found to have a significant association with many patient-related variables like age, disease duration and disease severity. Secondary Sjogren's syndrome was the most common extra-articular manifestation. Extra-articular manifestations are rarely reported by studies and thus large sample studies are needed to provide important insights into the course of RA patients.

Table 1. Baseline characteristics of the patients included in the study

Variables	Frequency	Percent
Age groups (in years)		
Less than 50	21	42.0%
> 50 to 70	22	44.0%
> 70	7	14.0%
Gender		
Females	39	78.0%
Males	11	22.0%
Disease duration (in years)		
$\leq$ 15	31	62.0%
> 15	19	38.0%

Co-morbidities		
Hypertension	11	22.0%
Coronary Artery Disease	7	14.0%
Diabetes Mellitus	6	12.0%
Hypothyroidism	6	12.0%
Others	3	6.0%
Serology		
Rheumatoid factors	44	88.0%
Anti-CCP	38	76.0%
Anti-neutrophilic antibody	27	54.0%
Disease Activity Score 28		
Mild (<3.2)	11	22.0%
Moderate (3.2 to 5.1)	13	26.0%
Severe (>5.1)	26	52.0%

Table 2. Distribution of extra-articular manifestations of RA in our patient population

Extra-articular manifestations	Frequency	Percent
Secondary Sjogren's syndrome	11	22.0%
Osteoporosis	9	18.0%
Interstitial lung disease	8	15.5%
Nodules	6	12.0%
Fibromyalgia	5	10.0%
Coronary Artery Disease	4	8.0%
Peripheral neuropathy	3	6.0%
Vasculitis	2	3.0%
Eye manifestations	1	2.0%
Malignancy	1	1.0%
Amyloidosis	1	1.0%

Table 3. Association of patient related variables with the presence of any extra-articular manifestation

	Any extra-articular anifestations		
	Yes =14	No = 36	p value
Age group			
Less than 50	2	19	
> 50 to 70	5	17	<0.01
> 70	7	0	
Gender			
Females	10	29	0.48
Males	4	7	
Disease duration (in years)			
$\leq$ 15	2	29	<0.01
> 15	12	7	
DAS 28			
Mild (<3.2)	1	10	
Moderate (3.2 to 5.1)	1	12	<0.01
Severe (>5.1)	12	14	

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