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Extra-articular manifestations of rheumatoid arthritis: Results of a university hospital of 526 patients in Turkey

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ABSTRACT

Objective. *Presence of extra-articular manifestations (EAM) in rheumatoid arthritis (RA) is associated with more severe disease and increased mortality. Prevalence of EAM may vary in different geographic areas and in different ethnic populations. In this study we investigated the frequency of EAM in 526 RA patients from a single university hospital in Turkey.*

Methods. *The hospital records of patients who had been diagnosed as RA in Hacettepe University Department of Rheumatology between the years 1988 and 2003 were retrospectively evaluated. There were 73 males and 453 females, and mean age of the patients was 48.0 ± 12.3 years. The mean follow-up period was 4.8 ± 4.1 years. Three hundred and fifty-nine patients were rheumatoid factor (RF) positive (68.3%).*

Results. *The overall frequency of EAM was 38.4% (202 patients). The most common EAM was rheumatoid nodules (18.1%). Sicca symptoms, pulmonary findings, Raynaud's phenomenon, livedo reticularis, carpal tunnel syndrome, vasculitis, amyloidosis, and Felty syndrome were present in 11.4%, 4.8%, 3%, 4.8%, 2.8%, 1.3%, 1.1%, and 0.3% of the patients, respectively. Overall EAM and rheumatoid nodules were significantly more common in RF positive patients than RF negative patients. The frequency of rheumatoid nodules was significantly higher in males than in females.*

Conclusion. *The prevalence of EAM in Turkey is higher than East Asia and Africa, and lower than UK and North America. Excluding secondary Sjögren's syndrome, our results are similar to other Mediterranean populations like Italy.*

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory and progressive disease characterized by various extra-articular manifestations (EAM). Presence of EAM is associated with more severe disease, higher rheumatic factor levels, and is considered as a risk factor for early death in patients with RA (1, 2). Prevalence of EAM may vary in different geographic areas and in different ethnic populations (2-8). To our knowledge, an analysis of the prevalence of EAM in a large cohort of Turkish RA patients has not been reported yet. In this study we investigated the frequency of EAM in 526 RA patients from a single university hospital in Turkey.

Patients and methods

The hospital records of patients who had been diagnosed as RA in Hacettepe University Department of Rheumatology between the years 1988 and 2003 were retrospectively evaluated. A total of 526 patients were included in this study. All of those patients fulfilled the ARA criteria for RA (9). There were 73 males and 453 females, and mean age of the patients was 48.0 ± 12.3 years (min-max: 17-82). The mean follow-up period was 4.8 ± 4.1 years. All patients were treated with combination of disease modifying drugs (DMARD), and no patient was given anti-cytokine agents. The patients also used low dose corticosteroids (i.e. < 6 mgr methyprednisolone per day). The dose of corticosteroids was increased when indicated, such as the presence of vasculitis.

All of those patients had undergone complete physical examination and complete medical history. Complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, rheumatoid factor (RF), urine analysis, and blood biochemistry were routinely checked. Three hundred and fifty-nine patients were RF positive (68.3%). All patients who were tested negative for RF had normal sacroiliac joint radiography, and negative for a history of psoriasis. The diagnoses of EAM were confirmed by chest radiograms, thorax high resolution computed tomography, abdominal ultrasonography, pulmonary function tests, neurophysiologic studies, Schirmer's test, and/or pathologic examination.

The Statistical Package for Social Sciences (SPSS), v 10.0 for Windows, and Graphpad Instat were used to analyze the data. The frequencies of EAM were compared between males and females, and between RF positive and negative patients by using the χ^2 test and Fisher's exact χ^2 test. A p value < 0.05 was

Table I. Prevalence of extra-articular manifestations in our patients with rheumatoid arthritis (n = 526).

Extra-articular manifestation	Number of patients	Percentage
Rheumatoid nodule	95	18.1%
Sicca symptoms	60	11.4%
Pulmonary findings	25	4.8%
Raynaud's phenomenon	16	3%
Livedo reticularis	25	4.8%
Carpal tunnel syndrome	15	2.8%
Vasculitis	7	1.3%
Amyloidosis	6	1.1%
Felty syndrome	2	0.3%
Overall	202	38.4%

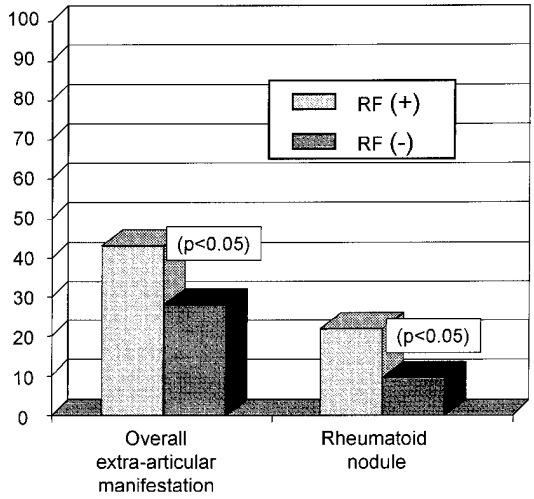

Fig. 1. Prevalence of overall extra-articular manifestations and rheumatoid nodules in rheumatoid factor (RF) positive rheumatoid arthritis (RA) patients and RF negative RA patients.

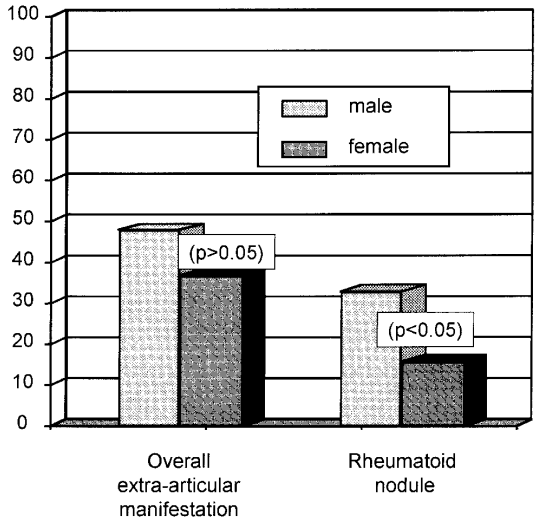

Fig. 2. Prevalence of overall extra-articular manifestations and rheumatoid nodules in male rheumatoid arthritis (RA) patients and female RA patients.

considered statistically significant.

Results

The overall frequency of EAM was 38.4% (202 patients). The most common EAM was rheumatoid nodules, which was identified in 95 patients (18.1%). Sicca symptoms were present in 60 patients (11.4%). The diagnosis of secondary Sjögren's syndrome was made in 28 of those patients (5.3%). Twenty-five patients (4.8%) had pulmonary findings such as pleurisy, interstitial fibrosis and rheumatoid lung nodules. Livedo reticularis was detected in 25 patients (4.8%), Raynaud's phenomenon in 16 patients (3%), and carpal tunnel syndrome in 15 patients (2.8%). Seven patients had findings of vasculitis such as polyneuropathy, cutaneous ulceration, or palpable purpura (1.3%). Amyloidosis developed in 6 patients (1.1%), and Felty syndrome was diagnosed in 2 patients (0.3%) (Table I).

The frequencies of EAM were evaluated according to the gender of the patient and RF status. The overall frequency of EAM was 155/359 (43.2%) in RF positive patients and 47/167 (28.1%) in RF negative patients ($p < 0.05$). The frequency of rheumatoid nodules was 79/359 (22%) in RF positive patients and 16/167 (9.6%) in RF negative patients ($p < 0.001$) (Fig. 1). The overall frequency of EAM was 35/73 (47.9%) in male patients and 167/453 (36.9%) in female patients. Although EAMs are apparently higher in males, the difference did not reach to a statistically significant level. The frequency of rheumatoid nodules was 24/73 (32.9%) in male patients and 71/453 (15.7%) in female patients ($p<0.001$) (Fig. 2).

Discussion

EAM of RA is of clinical importance since presence of those clinical findings correlate with articular severity, functional impairment, and increased mortality (1, 2). The prevalence of EAM shows variations in different geographical areas. RA patients in Eastern Asian or African countries like Malaysia, China, and Nigeria have significantly fewer EAM than RA patients in UK, US and Canada (2, 4-7). For instance, rheumatoid nodules were seen in only 1% of RA patients in Nigeria (6), and in 4.6% of RA patients in China (5), while this finding was present in 53% of RA patients in Canada (7), 51.4% of RA patients in UK (8), and 39.4% of RA patients in US (2). The overall frequency of EAM was 76% in Canada, 66.4% in UK, and 57.1% in US (2, 7, 8). Hence, EAM of RA appears more frequent in the Northern Europe and North America. EAM in the Mediterranean basin shows an intermediate prevalence between those geographical areas. A recent Italian

study extensively evaluated a large cohort of RA patients (n = 587) (3). Prevalence of overall EAM was 40.9%, and the most common EAM were sicca syndrome and rheumatoid nodules, being present in 17.5% and 16.7% of the Italian RA patients, respectively (3). Frequencies of overall EAM and rheumatoid nodules are quite similar in our patients. However, sicca syndrome appears less frequent in our group. Although sicca symptoms were present in 11.4%, the diagnosis of secondary Sjögren's syndrome was confirmed in only 5.3%. Detection of sicca syndrome depends to a great extent on the method of investigation. In general, a retrospective study like ours may give a lower estimate of the incidence of conditions that have to be actively searched for, in contrast to disease manifestations that are easily detectable in the clinic, such as rheumatoid nodules. Overall prevalence of EAM was 46.2% and of rheumatoid nodules was 10.6% in a smaller study from Turkey (10). However, the frequency of secondary Sjögren's syndrome was not mentioned in this study. Therefore, the exact prevalence of Sjögren's syndrome in Turkish RA patients requires further investigations.

Prevalence of secondary Sjögren's syndrome appears higher in Greece, another Mediterranean country and geographic neighbor of Turkey. The frequency of sicca syndrome was 39.8% and 32.8% in two different studies from Greece (8, 11). The reason for this difference remains unclear. Rheumatoid nodules were reported in 5.6% and 11.5% of RA patients in those studies. The prevalence of overall EAM was 20.4% in the former study. Excluding secondary Sjögren's syndrome, 45.4% of all patients had at least one EAM in the latter study. However, patients with anemia of chronic disease were regarded as "EAM". Therefore, the definition of "EAM" remains inconsistent, and a true comparison is not possible.

One of the possible reasons underling different prevalence of EAM among different populations could be genetic diversity. The association of RA with human leukocyte antigen (HLA) DR4 has been confirmed in many populations. Moreover, there is evidence that certain HLA alleles could be associated with extra-articular involvement in RA (12-18). On the contrary, the association between HLA alleles and extra-articular involvement could not be confirmed in other studies (11, 19-21). Likewise, two recent studies from Turkey failed to find any association between EAM prevalence and HLA (10, 22). Therefore, the importance of HLA as a genetic marker determining disease phenotype in RA patients, including EAM, requires further study.

Environmental factors could contribute to the development of RA and its EAM. Infectious agents have long been proposed as etiologic agents in RA (23, 24). On the other hand, bacterial and parasitic infections during childhood may determine a protective effect against RA by inducing tolerance to the postulated infective trigger (25). Dietary habits may play a role in the regulation of inflammatory reactions (26, 27). Smoking appears as a risk factor for nodule development in RA patients (1, 28, 29). A warm climate and sunlight may modulate the immune response (30). However, determining the potential roles of these environmental factors in the occurrence of EAM in RA is a very difficult and complicated issue, and requires much more effort.

Presence of RF is a risk factor for more aggressive disease course and increased prevalence of extra-articular involvement in previous studies (1). EAM, specifically rheumatoid nodules are also more common in male patients (1, 3, 31, 32), although conflicting data exist (33). In our study, overall EAM and rheumatoid nodules were significantly more frequent in RF positive patients, and rheumatoid nodules are significantly more common in men.

An interesting finding in our study is the female to male ratio (453/73). This figure appears higher than previously reported in the literature, which was approximately 2:1 to 4:1 (1-22). Our clinic is the main referral center for rheumatic diseases in central Anatolia, and to our knowledge our study represents the largest RA series in our country. In contrast to our results, smaller series from Turkey revealed a female to male ratio of 4:1 (10, 22). The reason for this unique difference remains to be established.

In conclusion, we demonstrated that the prevalence of EAM in Turkey is higher than East Asia and Africa, and lower than UK and North America. Excluding secondary Sjögren's syndrome, our results are similar to other Mediterranean populations like Italy. However, our study was retrospective and presents the usual limitations of a retrospective case-control design. For instance, we could not evaluate peripheral joint damage using Larsen or Sharp's score. Moreover, some important variables were not addressed, such as cigarette smoking and educational status. Furthermore, one of the possible reasons underlying varying prevalence of EAM in different studies may be the different level of diagnostic investigation. Therefore, further prospective studies using standard criteria for the definition and evaluation of "EAM" are needed to determine the exact prevalence of EAM of RA in different genetic populations and in different geographical areas. Identification of the phenotypic properties of RA in different populations and mechanisms causing the difference in the prevalence of EAM of RA may help us enlighten the pathobiology of this disease with the hope of developing novel therapeutic approaches.

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