EXTRA-ARTICULAR MANIFESTATIONS OF SERONEGATIVE AND SEROPOSITIVE RHEUMATOID ARTHRITIS

Vjollca Sahatçiu-Meka[1]*, Sylejman Rexhepi[2], Suzana Manxhuka-Kërliu[3], Mjellma Rexhepi[2]

[1] Physical Medicine Department, Clinic for Orthopaedics, Faculty of Medicine, University of Prishtina, Mother Theresa st., 10000 Prishtina, Kosovo

[2] Rheumatology Department, Clinic for Internal Medicine, Faculty of Medicine, University of Prishtina, Mother Theresa st., 10000 Prishtina, Kosovo

[3] Institute for Pathology, Faculty of Medicine, University of Prishtina, Mother Theresa st., 10000 Prishtina, Kosovo

* Corresponding author

Abstract

Although considered a "joint disease," rheumatoid arthritis is associated with the involvement of extra-articular manifestations. The aim of the study is the investigation and comparison of frequency and type of extra-articular manifestations in a well defined community based cohort of patients with seropositive and seronegative rheumatoid arthritis. Using the ACR (1987) criteria for rheumatoid arthritis, patients have been classified into the 2nd and 3rd functional class (ARA). The studied group consisted of 125 seronegative patients with titters lower than 1:64 as defined by Rose-Waaler test, whereas the control group consisted of 125 seropositive patients with titters of 1:64 or higher. All patients were between 25-60 years of age (Xb=49,96), with disease duration between 1-27 years (Xb=6,41). In order to present the findings of the study, the structure, prevalence, arithmetic mean (Xb), standard deviation (SB), variation quotient (QV%) and variation interval (Rmax-Rmin) have been used. Probability level has been expressed by $p<0,01$ and $p<0,05$. Correlation between the number of extra-articular manifestations and duration of the disease has been calculated by means of Pearson linear correlation. Higher presence of diffuse lung fibrosis, central and peripheral nervous system damages have been confirmed in the seropositive group, and osteoporosis in the seronegative; however, no statistical difference has been found. In extra-articular manifestations, "rheumatoid core" in the seropositive subset ($\chi^2=4,80$, $p<0,05$) presented significant statistical difference. Rheumatoid nodules were more frequent in seropositive subset (12%:16%), in both sexes; however, they were not of significant statistical difference. Neuropathy and lung diseases were also frequently present in seropositive group, but no statistical difference has been found regarding the statistical difference. Longer duration of the disease resulted in an increase of the number of extra-articular manifestations. Calculated linear correlation by Pearson, resulted as positive and high correlation in total ($r=0,36$, $p<0,01$), and for groups [($r=0,52$, $p<0,01$) seronegative, ($r=0,25$, $p<0,01$) seropositive], nevertheless no significant statistical difference was found regarding the sero-status. In conclusion, extra-articular manifestations are more frequent in the seropositive patients. The longer the duration of the disease the larger the number of extra-articular manifestations. Differences with regard to sero-status and sex, with some exceptions, are not observed.

KEY WORDS: rheumatoid arthritis, seropositive, seronegative, extra-articular manifestations.

Introduction

Rheumatoid arthritis (RA) is recognised to be an autoimmune disease with the unknown etiopathogenesis that causes preclinical systemic abnormalities and eventually leads to synovial inflammation and destruction of the joint architecture (RA is one of the most prevalent connective tissue diseases and can be complicated by vasculitis with systemic manifestations (1,2,3). The majority of scientists support the immunology based theory on discovery of Rheumatoid Factor (RF) (4). Rheumatoid Factor is an antiimunglobuline with a course against fragment Fc of IgG human molecule, but is not a pathognomonic sign of RA since it may be present in patients with different inflammatory disorders, as well as in 5%-8% in healthy population; however it could be considered as a parameter for immunological activity. People without symptoms, with persistently increased RF are more predisposed to developing RA. In some studies, generation of RF is associated with a presence of HLA-DR4 and DRB1. Rheumatoid Factor could be in different immunoglobuline classes (G, A, D and E) defined by ELIZA (2). Recently, various test methods based on the principle of agglutination (Waaler-Rose and Latex tests) are being applied, by which only the presence of RFIgM is proven. Rheumatoid Factor is present 70% - 80% in patients with RA, where the disease is defined as a seropositive athropaty (5). The endothelium, lining the blood vessels, becomes activated during the inflammatory process, resulting in the production of several mediators, the occurrence of endothelial adhesion molecules, as well as in increased vascular permeability (6). Extra-articular manifestation in RA are present in 10-20% of patients and are more frequent in seropositive male patients. Rheumatoid vasculitis affects a subset of patients with established RA (approximately 1 to 5%) (2). Anaemia is a frequent extra-articular manifestation in RA (7). Rheumatoid nodules as exclusive extra-articular manifestation of RA, definitely are part of the registered diagnostic 1958 and revised ARA criteria 1987 (2,3). Inflammation and autoimmunity are associated with increased cardiovascular risk in patients with RA. Cardiovascular disease is the leading cause of death in patients with RA (8). Lung disease is the most frequent and among the most severe extra-articular manifestations of RA. Pleuropulmonary manifestations in connective tissue diseases are frequent and variable (9). Entrapment neuropathy of the upper extremities could be detected by electroneurophysiological investigations in one third of patients with RA (10). Dermatological involvement tends to occur in patients with more severe RA, but may be associated not only with seropositive RA, as is often described in the literature, but also with seronegative RA (2).

Aim

The aim of this study is to investigate and compare the frequency and type of extra-articular manifestations and the correlation between the number of ExRA and the duration of the disease in a well defined community based cohort of patients with seropositive and seronegative rheumatoid arthritis.

Materials and Methods

Patients

Patients have been classified according to ACR (1987) criteria for rheumatoid arthritis and all belonged to 2nd and 3rd functional class (ARA). In this study, conducted within the period between 2000 - 2008, 250 patients with disease onset, diagnosed as seropositive and seronegative were examined at the Clinic of Sports Medicine in Prishtina and at Internal facilities in Kosovo. The test group consisted of 125 seronegative patients (93 female, 32 male) with titters lower than 1:64, as defined by Waaler-Rose test. The control group consisted of 125 seropositive patients (93 female, 32 male) with titters of 1:64 or higher. The presence of RFIgM in serum was evaluated by standard test methods based on principle of agglutination (Waaler–Rose and Latex tests). As seronegativity was considered titter lower than 1/64 defined by Waaler-Rose test and titter 1/40 defined by Latex test. All patients were between 25-60 years of age (Xb=49,96). Average duration of the disease was Xb=46,63, SD=10,31 years in seronegative patients and Xb=47,30, SD=10,47 in seropositive. Duration of the disease in total was between 1-30 years (Xb=6,41), but the majority of patients displayed a duration between 1-5 years. Selected clinical signs to be explored were: frequency and type of extra-articular manifestation and correlation between the number of extra-articular manifestations and the duration of the disease. Statistical parameters used for the presentation of the results: structure, prevalence, arithmetic average (Xb), standard deviation (SD), variation coefficient (CV %) and variation interval (Rmax-Rmin). T-test and χ^2 test were used to determine differences between factors or features. Probability level was expressed by $p<0,01$ and $p<0,05$. Relationship between the variables was measured by Pearson linear correlation.

Extra-articular manifestation	Female				Male				Total			
	SNRA		SPRA		ARSN		ARSN		SNRA		SNRA	
	N	%	N	%	N	%	N	%	N	%	N	%
Muscular weakness	70	75,3	74	79,6	21	65,6	26	81,3	91	72,8	100	80,0
Muscular hypotrophy	45	48,4	50	53,8	12	37,5	14	43,8	57	45,6	64	51,2
Rheumatoid nodules	14	15,1	16	17,2	1	3,1	4	12,5	15	12,0	20	16,0
Scleritis	5	5,4	5	5,4	1	3,1			6	4,8	5	4,0
Conjunctivitis	3	3,2	4	4,3	1	3,1	6	18,8	4	3,2	10	8,0
Osteoporosis	51	54,8	39	41,9	5	15,6	10	31,3	56	44,8	49	39,2
Pleuritis	5	5,4	8	8,6	1	3,1	3	9,4	6	4,8	11	8,8
Sy.Caplan					1	3,1	3	9,4	1	0,8	3	2,4
Diffuse fibrosis *	7	7,5	10	10,8	2	6,3	5	15,6	9	7,2	15	12,0
CNS injures**	2	2,2	5	5,4	2	6,3	6	18,8	4	3,2	11	8,8
PNS injures ***	18	19,4	20	21,5	3	9,4	7	21,9	21	16,8	27	21,6
Anaemia	68	73,1	70	75,3	21	65,6	17	53,1	89	97,8	87	87,0
Vasculitis - purpura	13	14,0	10	10,8	2	6,3	3	9,4	15	12,0	13	10,4
Articular infection	20	21,5	17	18,3	2	6,3	8	25,0	22	17,6	25	20,0
" Rheumatoid core "	8	8,6	16	17,2	1	3,1	5	15,6	9	7,2	21	16,8

(χ^2=4,80, P<0,05)

*(lung), **(Central nervous system), ***(Peripheral nervous system).

TABLE 1. Extra-articular manifestation of RA with regard to sero-status and sex

Results

In both subsets (Table 1) muscular weakness [91 (72,8%) seronegative, 100 (80%) seropositive] and anaemia [89 (97,8%) seronegative, 87 (87%) seropositive] had higher frequency of incidence. Diffuse lung fibroses (7,2%:12%), central (3,2%:8,8%) and peripheral (16,8%:21,6%) nervous system injuries confirmed higher presence in seropositive patients, while osteoporosis (44,8%:39,2%) in seronegative; however only "Rheumatoid core" in seropositive subset (7,2%:16,8%, χ^2=4,80, p<0,05). displayed statistical difference. Rheumatoid nodules although with a higher presence in seropositive subset (12%:16%) in both sexes, did not show any significant statistical difference. Extra-articular manifestations (Table. 2) were present in 231 patient, or 92,4% of examinees. Regarding the sero-status, more frequent were seropositive 96, 8% versus 88% seronegative, with a significant difference (p<0,05). The duration of the disease was significantly longer in patients with ExRA (6,7 years, versus 2,9 years in patients without ExRA, and this difference was statistically significant (p<0,01). Regarding the sero-status, the duration of the disease was longer in patients with ExRA in both subsets, showing a high significance (p<0,01) although the difference was greater in seronegative group (7,0 years, vs. 2,7 years) than in seropositive (6,5 years vs. 3,8 years).

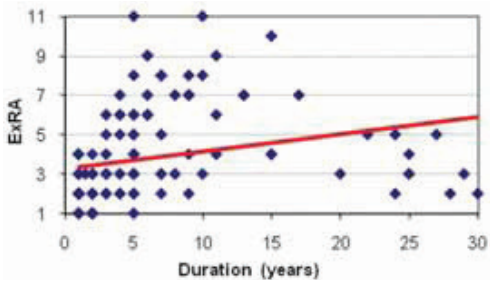
The duration of the disease (Table 3) was significantly higher in patients with 5 and more ExRA (9,8 years) than in patients with 1 - 4 ExRA (5,2 years), (t=5,13, p<0,01). Calculated linear correlation by Pearson between these two features, resulted with high positive correlation in total (r=0,36, p<0,01) and in groups [(r=0,52, p<0,01) seronegative, (r=0,25, p<0,01) seropositive], but regarding the sero-status, no significant statistical difference was found. Longer duration of the disease was accompanied by an increase in number of extra-articular manifestations (Figure 1, 2).

ExRA	SNRA				SPRA				Total					
	Examinees	Duration of the disease			Examinees	Duration of the disease				Duration of the disease			t=	p=
	N	%	Xb	SD	N	%	Xb	SD	N	%	Xb	SD		
With ExRA	110	88,0	7,0	6,2	121	96,8	6,5	7,0	231	92,4	6,7	6,6	0,59	P>0.05
Without ExRA	15	12,0	2,7	2,1	4	3,2	3,8	1,5	19	7,6	2,9	2,0	1,13	P>0.05
Total	125	100,0	6,5	6,0	125	100,0	6,4	6,9	250	100,0	6,4	6,5	0,11	P>0.05
T-test	t=	5,33	P<0,01	t=	2,74	P<0,01	t=	5,96	P<0,01			6,5	0,11	P>0.05
T-test	t=	5,33	P<0,01	t=	2,74	P<0,01	t=	5,96	P<0,01			12,0		

TABLE 2. Correlation between ExRA and the duration of the disease regarding the sero-status

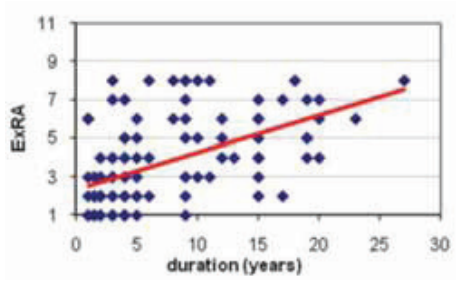
Number of ExRA	SNRA				SPRA				Total				t=	p=
	Examinees		Duration of the disease		Examinees		Duration of the disease		Examinees		Duration of the disease			
	N	%	Xb	SD	N	%	Xb	SD	N	%	Xb	SD		
1-4	73	66,4	5,0	4,8	83	68,6	5,4	7,4	156	67,5	5,2	6,3	0,37	P>0,05
5+	37	33,6	10,8	6,8	38	31,4	8,8	5,7	75	32,5	9,8	6,3	1,39	P>0,05
Total	110	100,0	7,0	6,2	121	100,0	6.5	7,0	231	100,0	6,7	6,6	0,59	P>0,05
T-test, 1-4/5+	t =	4,60	P<0,01		t =	2,75	P<0,01		t =	5,13	P<0,01			
Correlation	r =	0,52	P<0,01		r =	0,25	P<0,01		r =	0,36	P<0,01			
Regression	Y=0,19x+2,36				Y=0,09x+3,27				Y=0,13x+2,90					

TABLE 3. Correlation between the number of extra-articular manifestation and the duration of the disease with regard to sero-status



y= 0,09x + 3,27; R=0,25; T=2,75; P<0,01

FIGURE 1. Correlation between duration and ExRA in SPRA



y = 0,19x + 2,36; R=0,52; T=4,60; P<0,01

FIGURE 2. Correlation between duration and ExRA in SNRA

Discussion

Presence of ExRA in rheumatoid arthritis is associated with more severe disease and increased mortality. The factors that trigger the development of extra-articular features of RA are still unknown. HLA-DR alleles such as HLA-DR4 and HLA-DR1 are associated with the risk to develop RA. A large scale study from Sweden and the Mayo Clinic suggests that HLA-DR4, but not HLA-DR1, is associated with the risk to develop ExRA (11). Pai et al. (12) have found that the presence of RFIgA is accompanied with ExRA, while Cimmino et al. (13) in 587 patients with RA have confirmed a higher frequency of ExRA in seropositive patients, but without presence of ANA. In case of defined systemic vasculitis, synovitis has a light course or is inactive, associated with increased values of RFIgG (14). Some authors have noticed a high correlation between RFIgG and the active scale and frequency of ExRA (15). Presence of ExRA positively correlates with FRIgA and FRIgE levels (16). Recent studies suggest that RA is associated with interstitial lung disease (17). Respiratory system (lung diffuse fibrosis) of our seropositive patients was frequently affected but without statistical significance. In this sense, Balbir-Gurman (9), consider that pleural effusion is common in middle-aged men with RA and positive rheumatoid factor, and Ondrasik (18) has found that Caplan syndrome is more frequent in seropositive patients. Based on lung histological examinations, Enomoto et al. (19), exploring 911 breast radiograms, have found a significantly higher level of RFIgM and RFIgG in serum. Some authors consider that locally developed IgM and RFIgM in rheumatoid pleural are contributors in pathogenesis of this disorder (20). On the other hand, Unge et al. (21) did not find any significant statistical difference with regard to sero-status. The frequency of cardiovascular pathologies is higher in patients with RA. Wallberg et al. (22) have found that mortality in general, and as a consequence of cardiovascular diseases, was increased in case of seropositive RA. According to our data, statistical significance was found only in case of "rheumatoid core" in seropositive patients (χ^2=4.80, p<0.05). As regards this parameter, opinions diverge; Bologna et al. (23) have published a case when pericarditis was associated with a severe seronegative RA, in duration of 17 years, which clinical features of which were identical to constrictive pericarditis of different aetiology. Valkenborgh et al. (24) confirm that nearly all patients with pericarditis were rheumatoid arthritis factor positive, while valvular heart disease occurs in rheumatoid arthritis, usually as seronegative type. Differently, Wislowska et al. (25) ascertained that no differences in echocardiographic parameters values were observed between seropositive and seronegative persons. "Rheumatoid core" was frequently manifested in our seropositive patients of

both genders, but without any statistical significance. Valkenborgh et al. (24) confirmed that in the valvular group, female patients were more frequently affected. With regard to rheumatoid nodules, prevalence may vary in different geographic areas and in different ethnic populations. Some authors (26) have found a presence of rheumatoid nodules in value of 20-30% in white people; while for some countries outside Europe (Asia) the presence is lower 2-5% (27). Our patients had a frequency value of rheumatoid nodules approximately 16-20%, a value between that of Europe and Asia. Wisnieski et al. (28) have found that presence of rheumatoid nodules and RF correlate with severity of the disease. Different opinion have Maldonado et al. (29) regarding the outcome in a group of 16 patients with rheumatoid nodulosis that were followed over a period of 1-12 years. Six of these patients had an aggressive course and developed classic erosive polyarticular RA, while the others continued having episodic arthritis without erosive disease. Likewise, other authors confirmed the presence of rheumatoid nodules regardless duration of the disease or presence of the RF and that rheumatoid nodules could be present in patients with a light nonsystemic disease (30). Some authors confirmed the presence of rheumatoid nodules in seropositive patients (31) and in patients with the presence of DR4 (32). Rheumatoid nodules in our study were more frequent in seropositive subset (12%:16%), but this difference was not statistically significant, valid for both sexes. Highton et al. (33) suggest that the inflammatory process in the nodule and synovial membrane are likely to be similar, and that the characteristics of different tissues may be an important determinant of apparent differences between inflammatory lesions in synovial membrane and extra-articular nodules in RA. The existence of an autonomic neuropathy may be an important complicating factor in rheumatoid disease and may lead to increased morbidity and mortality. According to our data, central nervous system (CNS) and peripheral nervous system (PNS) injuries were more frequent in seropositive patient, while osteoporosis in seronegative. No significant statistical differences were observed between our seropositive and seronegative patients. Nadkar et al. (34) have found that one third of examinees suffered from neuropathy which did not correlate with RF. Presence of neuropathy in our patients was higher in seropositive subset, yet of no statistical significance.

Conclusion

Diffuse lung fibrosis, central and peripheral nervous system injuries, rheumatoid nodules, and neuropathy, were more frequently present in seropositive patients. With regard to sero-status only "rheumatoid core" was statistically significant. In conclusion, extra-articular manifestations are more frequent in the seropositive patients. The longer the duration of the disease the larger the number of extra-articular manifestations. Differences with regard to sero-status and sex, with some exceptions, are not observed.

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