EXTRA-ARTICULAR MANIFESTATIONS ASSOCIATED WITH SPONDYLOARTHRITIS

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Spondyloarthritis is a group of chronic diseases with axial, peripheral or mixed musculoskeletal manifestations, but also with extra-articular manifestations (EAM). EAM are common in this condition and are included in the diagnostic criteria. The present study is an observational, retrospective, cross-sectional study, performed on 105 patients. The aim of the study was to assess the prevalence of EAM in a group of patients diagnosed with ankylosing spondylitis and to identify possible differences in patient profile according to associated EAM. HLA-B27 antigen was positive in 76.2% of patients. The prevalence of EAM in the follow-up period in the patients in the study was 10.05%. The most common was uveitis (55.2%), followed by inflammatory bowel disease (28.6%) and psoriasis (21.0%). A positive correlation was observed between HLA B27-antigen, uveitis, men, and a positive correlation between women and inflammatory bowel disease. Biological treatment alone or in combination with conventional treatment was the the predominant choice and it was noted that it controls the disease more effectively than conventional treatment. The most common TNF inhibitors were adalimumab and infliximab.. The study confirmed the results reported in the literature regarding the dominance of males in ankylosing spondylitis, but with the inclination of the balance towards females in case of association with inflammatory bowel disease. EAM should be taken into consideration when choosing the subsequent therapeutic strategy.

Keywords: Spondyloarthropathies, extra-articular manifestation, therapeutic strategy.

INTRODUCTION

The term spondyloarthritis brings together a group of distinct chronic inflammatory diseases, which share clinical, genetic and pathophysiological characteristics[1]. Subtypes included under this term are ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis, psoriatic arthritis, reactive arthritis (ARe), spondyloarthritis associated with inflammatory bowel disease (IBD) and juvenile ankylosing spondylitis[2, 3]. The common features of SpA refer to inflammation of axial structures, peripheral manifestations (dactylitis, enthesitis, mono- or asymmetric oligoarthritis), extra-articular manifestations (EAM

anterior uveitis, psoriasis, inflammatory bowel disease) as well as the association with the HLA-B27 antigen[1, 4]. Depending on the clinical presentation, patients may fall into two major subtypes: axial spondyloarthritis, in which damage to the sacroiliac and/or vertebral joints predominates and peripheral spondyloarthritis, in which peripheral manifestations predominate[1]. Axial spondyloarthritis is further classified as radiographic (ankylosing spondylitis) or non-radiographic, while peripheral spondyloarthritis includes psoriatic arthritis, reactive arthritis, spondyloarthritis associated with IBD and juvenile spondyloarthritis[2, 5].

In AS, acute anterior uveitis is the most common EAM occurring in 33%–40% of patients and may precede spondylitis[6]. The decrease in

visual acuity during uveitis attacks in SpA is recorded in almost 60% of patients, but this is temporary, the ocular manifestations disappearing completely after each episode of uveitis[7]. Severe vision loss is rare and is associated with posterior uveitis and panuveitis, but they are rare in SpA[8]. Common complications are posterior synechiae, glaucoma, cataracts, macular edema and cystoid macular edema[9, 10].

Attacks are typical unilateral and manifested by pain, photophobia and hyperlacrimation. They also tend to affect often in the contralateral eye and can lead to cataracts or secondary glaucoma[9]. Topical tratment recomnded by ophtalmologist could be useful but the immunosuppressive treatment administrated by rheumatologist is mandatory. Sulfasalazine decreases the frequency, duration and severity of uveitis and can be used prophylactically[6]. The TNF blockers (infliximab, adalimumab, golimumab, certolizumab) prooved to be efficient regarding the uveitis control, while the etanercept, another TNF blocker is not approved for uveitis, as well as IL17 inhibitors –secukinumab.

Regarding IBD mcroscopic inflammation has been associated with the male sex, an early onset of axial SpA, a more accelerated progression of the disease, higher activity objectified by the BASDAI score (Bath Ankylosing Spondylitis Disease Activity Index), in the absence of any correlation with HLA-B27 status or other EAM[11]. The two possibilities are either Crohn's disease (CD) or ulcerative colitis (UC). Fecal calprotectin testing and endoscopic evaluation are required to support the diagnosis. Sulfasalazine is recomanded among the cases with peripheral involvement, dar rezult au fost incurajatoare si pt manif intestinale. The gold standard for those with IBD and SpA who cannot control the disease with csDMARDs is anti-TNF alpha therapy of which infliximab and adalimumab are the most widely used.

In 80% of cases the psoriasis lesions precede the arthritis, in 5–10% they start at the same time and in the rest of the cases the arthritis manifests itself first, which causes diagnostic difficulties. MTX is the original therapeutic standard for psoriasis and can be used in peripheral forms of the disease. The next therapeutic step after synthetic DMARDs is biological therapy.

All the TNF blockers are used in psoriasis arthropathy and perhaps with an even better response would be IL-17A inhibitors (secukinumab, ixekizumab), IL-12/IL-23 inhibitors (ustekinumab) and selective phosphodiesterase 4 inhibitor-Apremilast[12].

Other EAM are represented by cardiovascular diseases (Isolated Aortic Regurgitation, Atrioventricular block or Bundle Branch Block, Aortitis), pulmonary disease (apical fibrosis, interstitial lung disease, ventilatory dysfunction secondary to thoracic restriction, sleep apnea and spontaneous pneumothorax)[13], kidney disease (secondary amyloidosis and nephropathy with immunoglobulin A) and hearing loss, but these EAM are less common. Overall, cardiovascular disease can reach a prevalence of up to 64% in patients with AS, leading to an increased level of heart failure and stroke in these patients[14]. In an autoimmune disease, namely systemic lupus erythematosus, cardiovascular disease accounts for about 35% of patient mortality[15].

OBJECTIVES

The main objective of this study was to evaluate the prevalence of EAM in a group of patients diagnosed with AS. The secondary objectives were to compare the different clinical forms (axial, peripheral and mixed) and major EAM (uveitis, inflammatory bowel disease, psoriasis), to find out the frequency of complications associated with the disease and also to highlight the possible correlations between the severity of the symptoms, the type of treatment, the level of inflammation and also to observe the distribution of patients according to sex and age.

MATERIALS AND METHODS

To carry out this work, an analytical, observational, retrospective, cross-sectional type of study was performed on a group of 105 patients admitted to the Internal Medicine Clinic and Rheumatology of the Clinical Hospital „Dr. Ion Cantacuzino" Bucharest on October 1, 2018–July 12, 2019, who were diagnosed with AS and had EAM . The data was collected in an anonymously way; the security and confidentiality were respected, the informations collected from this group of patients being used only for research purposes. The study was approved by the local ethics commission.

The criteria for including patients in this study are: the age over 18 years, Caucasian race, having the diagnosis of AS, the association of at least one EAM documented in the literature.

The evaluated variables were represented by demographic and anthropometric data, characteris-

tics of spondyloarthritis, markers of inflammation, disease activity, description of EAM, the type of treatment used.

Data distribution was assessed with the Kolmogorov-Smirnov test with the Lilliefors correction. Continuous variables were reported as mean ± standard deviation, and discrete variables were expressed as absolute numbers (percentage frequency). Discrete data were analyzed with the Chi-Square test. The degree of association between the variables was assessed with the Spearman test of the correlation of the difference in ranks for ordinal data. Statistical significance was considered to be present if $p < 0.05$. Statistical analysis was performed using Microsoft Excel 2013.

RESULTS

During the study period, we identified 1044 patients diagnosed with AS, of whom 105 had EAM and formed the study group. The prevalence of EAM was 10.05%. The majority of the study group was represented by men (65.7%, $p < 0.001$), aged 40–60 years (53.3%, $p < 0.001$) and overweight (46.7%, $p < 0.001$). Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a validated score for assessing disease activity in AS. The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite index used to assess disease activity in SpA. According to BASDAI and ASDAS-CRP score, most patients in our study were in remission or had low disease activity.

The HLA-B27 antigen was positive in a proportion of 76.2% ($p < 0.001$); HLA-B27 antigen was negative in 12.4%, and the remaining 11.4% had no HLA-B27 antigen determined.

The mean age at diagnosis was 33.5 ± 13.3 years. According to BASDAI and ASDAS-CRP scores, most patients were in remission or had low disease activity (41.9% had BASDAI <4 and 37.2% had ASDAS CRP <2.1). Conventional treatment (nonsteroidal or steroidal anti-inflammatory medication, sulfasalazine, methotrexate) was prescribed to 38.1% of patients; biological therapy was administered alone in 29.5% of patients and 25.7% of patients had both types of therapies.

The most common EAM were the following: acute anterior uveitis (55.2%, $p < 0.001$), IBD (28.6%) and psoriasis (21.0%). Some EAM considered rare, were found in only 13 patients as follows: 4 cases of aortic insufficiency, 3 cases of branch block, 2 cases of pulmonary fibrosis, 2 cases of neurosensory hearing loss, 1 case of erythema nodosum and 1 case of renal amyloidosis. Of these, 9 were associated with one of the frequent EAM and 4 on their own. No cases of circadian balanitis, gonorrhea keratoderma, atrioventricular block, aortitis or IgA nephropathy have been reported. In order to find out the prevalence of various EAM in patients with AS in general, they should be related to the total number of patients in the group. These values are 5.6% for uveitis, 2.9% for IBD and 2.1% for psoriasis.

Table 1

General characteristics of patients with AS

Age (yeaars) – mean ± SD	20-40	40-60	60-80		p value[1]
46.4±13.1	32 (30.5)	56(53.3)	17(16.2)		<0.001*
Sex, N(%)	Women	Male			
	36(34.3)	69(65.7)			0.001*
BMI(kg/m^2) – mean ± SD	Underweight, N(%)	Normal weight, N(%)	Overweight, N(%)	Obesity, N(%)	
27.2 ± 4.8	4(3.8)	27(25.7)	49(46.7)	25(23.8)	<0.001*
HLA-B27, N(%)	Pozitive	Negative	Unknown		
	80(76.2)	13(12.4)	12(11.4)		<0.001*
BASDAI – mean ± SD	<4	≥4	Unknown		
3.2 ± 2.7	44(41.9)	29(27.6)	32(30.5)		0.079
ASDAS – mean ± SD	<1.3	1.3-2.1	2.1-3.5	>3.5	
2.2 ± 1.7	26(24.8)	13(12.4)	12(11.4)	14(13.3)	0.048*
EAM	Uveitis	IBD	Psoriazis	More than one[2]	
	58(55.2)	30(28.6)	22(21.0)	17(16.2)	<0.001*
Treatment, N(%)	DMARDs[3]	Biological therapy	Both		
	40(38.1)	31(29.5)	27(25.7)		0.257

1. *Chi Square test* result *(* statistical significance at p <0.05)*.
2. Refers to two or more EAM in the same patient.
3. Does not include those with NSAIDs only when needed.

Table 2

Clinical data of patients with ankylosing spondylitis, global and separate according to the clinical form of the disease (axial, peripheral and mixed)

	AS	*Clinical form*			*p value[1]*
		Axial	*Mixt*	*Peripheric*	
Pacients, N(%)	105	46 (43.8)	54 (51.4)	5 (4.8)	<0.001*
CRP (mg/dl) – mean ± SD	14.8±25.1	11.4±19.4	18.7±29.8	4.3±3.1	0.167
BASDAI – mean ± SD	3.2±2.7	3.0±2.6	3.6±2.8	0.5±0.5	0.697
<4, N (%)	44 (41.9)	22 (47.8)	19 (35.2)	2 (40.0)	0.311
>4 N(%)	29 (27.6)	12 (26.1)	17 (31.5)	-	
ASDAS(CRP) – mean ± SD	2.2±1.7	1.9±1.3	2.5±1.9	1.3±0.8	0.430
<1.3 (inactive disease)	26 (24.8)	11 (23.9)	13 (24.1)	2 (40.0)	
1.3-2.1 (low disease activity)	13 (12.4)	7 (15.2)	6 (11.1)	-	0.503
2.1-3.5 (high disease activity)	12 (11.4)	6 (13.0)	5 (9.3)	1 (20.0)	
>3.5 (very high disease activity)	14 (13.3)	4 (8.7)	10 (18.5)	-	
EAM, N(%)					0.754
Anterior uveitis	58 (55.2)	25 (54.4)	31 (57.4)	2 (40.0)	
IBD	30 (28.6)	14 (30.4)	13 (24.1)	3 (60.0)	
Psoriasis	22 (21.0)	8 (17.4)	14 (25.9)	0	
Combinations[2]	15 (14.3)	7 (15.2)	8 (14.8)	0	
Treatment, N(%)					0.319
Without treatment[3]	7 (6.7)	5 (10.9)	2 (3.7)	0	
Conventional	40 (38.1)	15 (32.6)	22 (40.7)	3 (60.0)	
Biological therapy	31 (29.5)	16 (34.8)	14 (25.9)	1 (20.0)	
Both	27 (25.7)	10 (21.7)	16 (29.6)	1 (20.0)	

1. The result of the t test for continuous data with normal distribution, the Mann-Whitney test for continuous data with distribution abnormal or Chi Square test for discrete data. Only axial and mixed clinical forms were compared, with one being recorded too few peripheral patients. (*statistical significance at p <0.05).
2. It refers to two EAM in the same patient and includes the less common ones.
3. Patients who have a NSAIDs recommendation when needed.

Table 3

Demographic and clinical data of patients with AS, global and separate according to the main EAM (uveitis, BII and psoriasis) and the type of treatment at the time of discharge of patients with AS, globally and by categories of EAM

	AS	*EAM[1]*			*p value*
		Uveitis	IBD	Psoriasis	
Pacients, N(%)	105	49 (46.7)	26 (24.8)	17 (16.2)	<0.001*
Age (years) mean ± SD	46.4±13.1	43.1±14.1	47.4±10.2	50.5±11.4	0.087
Sex, N(%)					
women	36 (34.3)	13 (26.5)	15 (57.7)	6 (35.3)	0.029*
men	69 (65.7)	36 (73.5)	11 (42.3)	11 (64.7)	
BMI (kg/m^{2}) mean ± SD	27.2±4.8	26.2±4.4	27.8±5.7	29.8±4.3	0.027*
Underweight,N(%)	4 (3.8)	1 (2.0)	1 (3.9)	1 (5.9)	
normal weight,N(%)	27 (25.7)	18 (36.7)	7 (26.9)	0	
overweight,N(%)	49 (46.7)	23 (46.9)	11 (42.3)	7 (41.2)	
obese,N(%)	25 (23.8)	7 (14.3)	7 (26.9)	9 (53.0)	
ASDAS (CRP), N(%)	2.2±1.7	2.6±1.1	2.5±1.9	2.5±2.1	0.198
<1.3 (inactive disease)	26 (24.8)	14 (28.6)	5 (19.2)	6 (33.3)	
1.3-2.1 (low disease activity)	13 (12.4)	4 (8.2)	3 (11.5)	3 (16.7)	0.688
2.1-3.5 (high disease activity)	12 (11.4)	3 (6.1)	5 (19.2)	3 (16.7)	
>3.5 very high disease activity)	14 (13.3)	4 (8.2)	3 (11.5)	4 (22.2)	

Table 3 (continued)

Treatment, N(%)				
NSAID	23 (21.9)	9 (18.4)	5 (19.2)	6 (35.3)
Sulfasalazine	45 (42.9)	20 (40.8)	10 (38.5)	8 (47.1)
Methotrexate	11 (10.5)	2 (4.1)	4 (15.4)	4 (23.5)
Infliximab	14 (13.3)	8 (16.3)	4 (15.4)	1 (5.9)
Adalimumab	29 (27.6)	16 (32.7)	4 (15.4)	4 (23.5)
Etanercept	8 (7.6)	4 (8.2)	3 (11.5)	1 (5.9)
Golimumab	5 (4.8)	4 (8.2)	1 (3.8)	0
Certolizumab	1 (1.0)	0	0	0
Secukinumab	1 (1.0)	0	1 (3.8)	0

1. We excluded 9 patients who had associated uveitis and psoriasis or uveitis and IBD and also we excluded 4 patients who had: aortic insufficiency, hearing loss or pulmonary fibrosis.

Table 4

Correlations between sex, type of EAM and ocular complications, using the Spearman correlation test
(R values represent Spearman correlation coefficients, p values represent their significance level)

	Women	Male	Uveitis	Psoriazis
HLA-B27 antigen	$R=-0.256$	$R=0.256$	$R=0.352$	$R=-0.262$
	$p=0.008*$	$p=0.008*$	$p<0.001*$	$p=0.007*$
IBD	$R=0.209$			
	$P=0.032*$			
Uveita		$R=0.221$		
		$p=0.023*$		

Both the axial and the mixed clinical form presented uveitis as the most frequent EAM, followed by IBD and psoriasis. It should be noted that the peripheral form did not register cases of psoriasis. Within the axial form the conventional treatment had a proportion close to that of biological treatment (32.6% *vs.* 34.8%) and the associated treatment (conventional and biological therapy) ranked third (21.7%). Conventional treatment predominated in the mixed form (40.7%), followed by combined treatment (29.6%); biological treatment ranked last (25.9%).

Regarding the subgroups of EAM, the most common drug administered by conventional agent was sulfasalazine, in a total percentage of 42.9%, which also includes various associations with other conventional or biological agents.

A total of 54.3% of patients received treatment with anti-TNF alpha therapy, this figure including those with biological agents in combination with various conventional drugs. The most commonly used biological agent was adalimumab (27.6%) followed by infliximab (13.3%) and etanercept (7.6%). Golimumab (4.8%) and certolizumab (1.0%) had the lowest frequency.

Among the biological therapy, adalimumab dominated in the subgroup of uveitis (32.7%) and psoriasis (23.5%), and in the IBD group adalimumab was equal to infliximab (15.4%).

Patients diagnosed with acute anterior uveitis as EAM received mainly treatment with NSAIDs, Sulfasalazine (40.8%) and TNF blockers (65.3%), of which the most commonly used were adalimumab (32.7%) and infliximab (16.3%).

Patients who had an IBD as an EAM also received Sulfasalazine (38.5%), TNF blockers (46.2%) as the main treatment, with infliximab and adalimumab in equal proportions (15.4%), and only 19.2% of patients had NSAIDs in their treatment regimen.

Those patients who had psoriasis as EAM, 47.1% received Sulfasalazine and 23.5% received MTX. At the same time, 35.3% of cases received treatment with TNF blockers, with adalimumab being the main representative (23.5%).

In the present paper, uveitis has been positively correlated with HLA-B27 antigen and with males and negatively with females and psoriasis.

The gender distribution in the IBD category showed a higher ratio in the case of women, in a percentage that is statistically significant (57.7%, p <0.029).

The association of female with IBD and that of male with uveitis and HLA-B27 antigen has been confirmed.

DISSCUSION

Patients diagnosed with acute anterior uveitis as EAM received mainly treatment with NSAIDs, Sulfasalazine and TNF blockers (predominantly

adalimumab and infliximab). These findings are supported by other studies where where a similar distribution of the type of therapeutic agents used in the treatment of ocular complications is observed[16, 17].

Patients who had an IBD as an EAM received mostly sulfasalazine and TNF blockers, of which infliximab and adalimumab were used in equal proportions. These results are similar to some found in the literature, which attests to the very good effectiveness of treatment with TNF blockers[18].

In cases of EAM with psoriasis, almost half of the patients received sulfasalazine and almost a quarter received MTX. In terms of biological treatment, it has been used in over a third of cases, with adalimumab being the main representative. In other studies has been observed the use of a similar regimen. Sekukinumab has been approved for the treatment of psoriasis with good results, but in the study group it was used in only one patient[12].

The ratio of men to women in the present study is approximately 2:1, the proportion of males being 65.7% (p <0.001) according to the literature. Another study reported a similar ratio between men and women [19] and it has been noted in recent decades that the gender gap has narrowed[20].

HLA-B27 antigen was tested positive in the proportion of 76.2% (p <0.001) in our study group, this percentage being consistent with the frequency reported in the literature, namely 83%[21]. HLA-B27 antigen was negative and untested in 23.8% of patients. Similarly, Feldtkeller *et al.* found a similar prevalence[22].

The most common EAM found were acute anterior uveitis (55.2%, p <0.001), IBD (28.6%) and psoriasis (21.0%). In the literature the reported prevalences are higher and the order of frequency psoriasis third, as in our study[19, 23–25].

Aortic insufficiency, branch block, pulmonary fibrosis, neurosensory hearing loss, erythema nodosum and renal amyloidosis are EAM considered rare and they were found in only 13 patients in the study group. Aortic insufficiency has been reported with a frequency of about 2% at 10 years of evolution of AS, but this percentage increases to 12% after 30 years of evolution[26]. Atrioventricular or branch block occurs in approximately 5% of patients with AS[7]. Apical pulmonary fibrosis described in AS has a low incidence, reported between 1.3–30%[27]. Renal amyloidosis is one of the most important renal impairments in patients with AS, with a prevalence of 4%–8.6%[28].

It was observed a positive correlations between HLA-B27 antigen, uveitis and males, a positive correlation between females and IBD, and a negative one regarding HLA-B27 antigen with females and psoriasis. These corelation have been demonstrated to be statistically significant and have also been cited in other studies[20, 29–31].

CONCLUSIONS

The prevalence of EAM in the rheumatology clinic was 10.05%. The most common manifestation was uveitis which has been shown to correlate with HLA B27 antigen and men. IBD correlated positively with women and psoriasis correlated negatively with HLA-B27. EAM should be taken into consideration when choosing the subsequent therapeutic strategy.

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