Original paper

Extra-articular manifestations in ankylosing spondylitis: A single center analysis in Western Algeria

ABSTRACT:

Objective: Our objective was to analyze and assess the extra-articular manifestations (EAMs) associated with the ankylosing spondylitis in Western Algeria.

Methods: 292 patients diagnosed with AS at the level of rehabilitation department of Hassani Abdelkader Hospital of Sidi Bel Abbes region were enrolled. Studied parameters were: age, gender, disease duration, disease age onset, morning stiffness, joint involvements, laboratory data, disease activity, and treatments. All data were processed and analyzed via SPSS 22.0.

Results: One Hundred and Five (105) Algerian AS patients with extra-articular manifestations (EAMs) and 187 without EAMs were involved. The average disease duration was of 7.72 ± 4.970 and 6.55 ± 3.613 years in the EAMs and without EAMs groups, respectively. The group without EAMs suffered more from their lumbar (77%) and high inflammatory parameters (63.1% CRP positive), and most of them were smokers 20 (10.7%). However, EAMs patients' suffered the most from their joint (20% Vs 9.6 had knees affection and 41.9% Vs 25.7% had hips affection, respectively). High disease activity was more noted in EAMs group (52.4% VS 43.3%). Uveitis (AAU) and psoriasis (PsO) were the most common EAMs reported in AS patients and were significantly associated with radiological joint damage and duration morning stiffness $p<0.05$.

Conclusion: In AS Algerian patients, uveitis was the most common reported EAMs with higher radiological joint damage, high inflammatory parameters and high disease activity score.

Keywords : Ankylosing spondylitis (AS), Extra-articular manifestations(EAMs), Acute anterior uveitis (AAU), Psoriasis (PsO)

Introduction:

Ankylosing spondylitis (AS) is the most prominent form and the most frequent subtype of spondyloarthritis (SpA), with a prevalence ranging from 0.1 to 1.4% worldwide; males are more likely to be affected with a frequency of two to four times (Akkoç et al., 2017). AS comprises reactive arthritis, arthritis/spondylitis associated with psoriasis or with inflammatory bowel disease (IBD), and undifferentiated SpA (uSpA) (Rudwaleit, van der Heijde, et al., 2009). The most often cited SpA classification criteria is the European Spondylarthropathy Study Group (ESSG) criteria that was proposed in 1991 (Rudwaleit, 2004). Patients with AS often have extra-articular manifestations (EAMs), which are thought to be useful in the diagnosis of axial spondyloarthritis (axSpA)/AS (Man et al., 2021). Depending on the disease severity and SpA kind, the estimated prevalence of uveitis in SpA ranges in up to one-third of patients. In comparison to inflammatory bowel disease (IBD) (2%-9%) and psoriasis (7%-16%), ankylosing spondylitis (AS) is associated with a higher frequency of uveitis (20%–30%) (Juanola et al., 2016).

The objective of this study is to assess and analyze the extra-articular manifestations associated with the ankylosing spondylitis in Algerian patients.

Materials and Methods:

Population:

This cross-sectional studywas done at the level of Functional Rehabilitation and Internal Medicine departments of Hassani Abdelkader University Hospital of Sidi Bel Abbes region (Western Algeria) between 2018 and 2021 on the records of over 292 patients diagnosed with ankylosing spondylitis

Methods:

We looked at a variety of factors, including gender, age, disease duration, morning stiffness, medical history, articular and extra-articular injuries, laboratory data, and favorable outcomes; AS patients' HLAB27, disease activity markers, and treatment.

Statistical Analysis:

All data were processed and analyzed via SPSS 22.0 (Statistical Package for the 44 Social Sciences, IBM Corporation; Chicago, IL. August 2013). The Chi-square test was used for qualitative variables and the independent sample t-test for quantitative variables. Values are expressed as number (percentage) or mean ± standard deviation. Statistically significant differences were maintained when the p-value was less than or equal to 0.05 ($p \leq 0.05$).

Ethical approval: The Medical Committee of Sidi Bel Abbes University Hospital and Department of Biology, Djillali Liabes University approved the study.

Results:

Table 1 presents a comparison of the demographic, clinical, paraclinical and therapeutic characteristics of two groups: patients with EAMs (acute anterior uveitis AAU, PsO psoriasis) and patients without EAMs.

Of the total of 292 patients there were 105 AS patients with extra-articular manifestations (EAMs) and 187 without EAMs. The average disease duration was 7.72 ± 4.970 and 6.55 ± 3.613 years in the EAMs and without EAMs groups, respectively. In addition, no significant difference were recorded between the two groups in terms of sexe (p=0.82) and AS morning stiffness duration (23.10±24.123 vs 26.23±28.138 p=0.14). Positive CRP value was highly significant in the group without EAMs p=0.006 and positive (HLAB27) was noted in the both groups (74.3% in EAMS group and 69% in the group without EAMs). Cervical damage was more reported in EAMS group but with no significant difference (44.8% VS 37%). Besides, radiological joint damage was more noted in the EAMs group, with a significant difference between the two groups in knees and hips affection (p=0.012, p=0.004 respectively).

The scores of BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and ASDASCRP (Ankylosing Spondylitis Disease Activity Score) in the EAMs group were higher than those in the without EAMs (3.071±1.867 vs 2.872±1.929 and 2.770±1.246 vs 2.552±1.330 respectively). There was no significant difference in age, disease duration, disease age onset, and treatment between the both groups.

Acute anterior uveitis (AAU) was the most common EAM reported in AS patients (n=100), while psoriasis (PsO) was only recorded in 15 AS patients. The duration morning stiffness, positive CRP as well as knees and hips affection showed a significant association with uveitis p=0.044 , p=0.005, p=0.041 , p=0.002 respectively. Concerning psoriasis (PsO), we noted an association with: male sexe p=0.004, longer duration of morning stiffness p=0.032, positive HLAB27 p=0.030, tobacco and disease activity p<0.0001, affection of knees p=0.001 and BASDAI p=0.011 (table 2). Moreover, disease duration was higher in PsO group than in AAU group (09.00±5.979 years vs 07.68±4.960 years respectively) and disease age onset was lower in PsO group than in AAU group (29.53±9.461 years vs 32.20±10.504 years respectively). We noted as well that the PsO group was younger than AAU group (38.53±8.647 vs 40.12±12.229 respectively). Cervical damage was more noted in AAU group (46% vs 29.4%), however radiological joint damage was more reported in PsO group (41.2% vs 19% for knees affection and 52.9% vs 43% for hips affection). Similarly, disease BASDAI (4.658±2.438 vs 3.055±1.900) and ASDASCRP (3.853±1.409 vs 2.755±1.250) were higher in PsO group than in AAU group. There was no significant difference in treatment between AAU and groups PsO (Table 3).

Discussion:

The present study is one of the first in its kind focusing on the association between extra-articular manifestations (EAMs) and patients' characteristics with ankylosing spondylitis (AS) as it is the

first report linking a discriminative association of AAU versus PsO to structural progression in western Algeria.

Our study enrolled 115 patients with EAMs and 177 without EAMs, any significant association was noted between the two groups in term of the sexe p=0.82 as reported by (Man et al., 2021) (p= 0.317) and (Varkas et al., 2018) (p=NS). Looking at the difference between the two studied groups, (Man et al., 2021) found an association between age and AEMS p<0.0001, however (Derakhshan et al., 2020) did not highlight this kind association p=0.093 which concords with our findings p=0.980. Furthermore, any difference was reported between the two groups in terms of age onset and disease duration p=0.794, p=0.172; similar results were found by (Varkas et al., 2018) (p=NS) .

Concerning the joints involvement, knees and hips affection was associated significantly with EAMs p= 0.012 and p=0.004 respectively. Inflammation did not only affect spine but may also affect peripheral joints and enthuses, heart, lungs, large bowel and eyes (Lukas et al., 2009) . No differences between the two groups in term of the scores of BASDAI (p=0.935) and ASDASCRP were noted (p=0.083); however the scores were higher in the EAMs group than in group without EAMs (3.071 ± 1.867 vs. 2.872 ± 1.929 and 2.770 ± 1.246 vs. 2.552 ± 1.330, respectively), which agree with the findings of (Varkas et al., 2018) p=NS , nevertheless, other authors did not support these findings (Man et al., 2021) .

The biological treatment used by the patients in the study of (Man et al., 2021) did not show a positive relationship with EAMs p=0.122 which matched with our findings.

Acute anterior uveitis (AAU) is the most common form of uveitis, half of patients with anterior uveitis are human leucocyte antigen (HLA) B27 positive; several epidemiological studies have confirmed the high prevalence of systemic disease in patients with AAU (Fabiani et al., 2016) . Anterior uveitis (AU) is the most common extra articular manifestation in ankylosing spondylitis (AS). Actually, a recent meta-analysis described a cumulative incidence of around one in four patients (Lie et al., 2017) .

Psoriasis is a chronic inflammatory skin disease with a strong genetic predisposition and autoimmune pathogenic traits. The worldwide prevalence is about 2%, but it may vary according to regions. A lower prevalence is recorded in Asian and some African populations, and up to 11% in Caucasian and Scandinavian populations (Rendon & Schäkel, 2019) .

We found a prevalence of 34.24% of uveitis and 5.13% of psoriasis. In keeping with the findings of (Essers et al., 2015) where AAU and psoriasis were present in 18.0% and 4.1% of the patients, respectively. Furthermore, in the study of (Stolwijk et al., 2015) the pooled prevalence of AAU was 25.8%, while psoriasis was 9.3% . In a German cohort of 236 individuals, the prevalence of AAU and psoriasis in AS patients was respectively of 20.9%, 10.2% (Rudwaleit, Haibel, et al., 2009). Likewise, in a French cohort of 181 newly diagnosed AS patients, the prevalence of AAU and psoriasis was respectively of 11.4%, and 14.4%. To date, no definite theory has been offered to explain the associations of uveitis with psoriasis and psoriatic arthritis. The release of cytokines and other mediators produced in the inflamed uvea into the systemic circulation may increase the risk of psoriatic manifestations. In addition, Th1 cells, Th17 cells and certain cytokines are involved in the pathogeneses of uveitis and psoriasis/psoriatic arthritis. Moreover, the reason for the stronger association of uveitis with psoriatic arthritis than with psoriasis is not fully understood; it may be related to the greater frequency of HLA-B27 (related to uveitis) in patients with psoriatic arthritis than in those with psoriasis. Further molecular studies are required in order to elucidate the mechanisms underlying these associations (Chen et al., 2021).

In another hand; any positive correlation was found between AAU and disease duration p=0.294. Whereas, (Essers et al., 2015) underlined an associated between AAU and longer disease duration; this association could not be demonstrated for psoriasis, this suggests that psoriasis may already be present before the onset or before the diagnosis of AS or perhaps may even have contributed to its diagnosis . Same case with other characteristics in terms of gender, disease activity indices did not show a significant association which is consistent with the study of (Man et al., 2021).

The history of only AAU were positively associated with the positive CRP p=0.005. In their study, (Essers et al., 2015) showed that the patients with AAU suffered from higher inflammation, and was associated with longer symptom duration and greater age . For psoriasis, no such association could be found, similarly to (Varkas et al., 2018) who have observed significantly higher CRP measurements over time only in patients with AAU versus those with psoriasis. In fact, more than 37% of measurements reached ≥ 0.5 mg/dl in the group of patients with AAU versus 24.5% of patients with psoriasis (p=0.057); when compared to psoriasis, patients with AAU may simply experience greater inflammation development, which represents the difference in inflammation accumulation. Although our results suggest a link between the prevalence of AAU and CRP, they do not necessarily depict a cause-and-effect relationship. The development of AAU could also be an indication of long-term exposure to systemic inflammation .

Spondyloarthritides are a group of diverse illnesses that have some common clinical, radiological, and serological characteristics. Patients with PsA may also have inflammatory axial involvement, which is a defining hallmark of AS (Dougados et al., 2011). In the present study we demonstrated a relation between psoriasis and joints affection; those with a history of psoriasis were affected in their knees p=0.001. (Ocampo D & Gladman, 2019) (Winchester et al., 2012) (Haroon et al., 2016) demonstrated that psoriasis is a multisystemic, inflammatory skin condition that can affectmany areas of the body, but most commonly the extensor surfaces of theelbows and knees,the presence of HLA-C*06 was associated with a delayed onsetof PsA29, HLA-B*27:05:02 is associated with increased riskof enthesitis, dactylitis, and symmetric sacroiliitis, whereas HLAB*08:01:01 and HLA-C*07:01:01 haplotypes are associatedwith joint fusion and deformities ,asymmetrical sacroiliitis, and dactylitis , recent genome-wide association studies (GWAS) have identified SNPs near HLA-C, TNFRSF9, and LCE3A as more strongly associated with psoriasis , whereas SNPs near IL-23R and TNFAIP3 were more strongly associated with PsA. Other genes identified as potential biomarkers for PsA are NOTCH2NL, HAT1, CXCL10, and SETD2 . Our results showed a negative association between psoriasis and age (p=0.137), ASDAS (p=0.915) and positive one

with sexe (p=0.004), HLAB27 (p= 0.030) and BASDAI (p=0.011) which agree with the results of (Feld et al., 2020) .The study of (Varkas et al., 2018) showed that psoriasis was solely associated with HLA -B27 negativity with a 90% increased risk, and male gender with a 50% increased risk. The research' results show that there are differences in the overall exposure to systemic inflammation across the EAM spectrum in anklosing spondylitis; because these EAMs usually appear before a diagnosis, they may be an early warning sign of a disease's potential to worsen .

Patients with AAU use more drugs than those with psoriasis with no significant association as noted by (Feld et al., 2020).

However, there were certain limitations to our investigation, relatively related to few patients included in our study from just one center. At baseline, the multivariate analysis was not performed for those with a history of crohn disease due to the low number of patients (n =5).

Conclusion:

In this paper, the patients with AAU had higher positive CRP over time and a striking association between uveitis, psoriasis and affection of joints was found, which may be useful for proper clinical diagnosis of AS disease.

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Table 1 : Demographic , radiologic and laboratory data of AS patients based on EAMs

Characteristics (Mean±SD) or n(%)	With EAMs n=115	Without EAMs n=177	P value
Age	39.87±12.113	37.37±12.065	0.980
Sexe			
Males	52(49.5%)	73(39%)	0.82
females	53(50.5%)	114(61%)	
Disease age onset	31.91±10.425	30.69±10.540	0.794
Disease duration	7.72±4.970	6.55±3.613	0.172
Duration morning stiffness	23.10±24.123	26.23±28.138	0.14
Spine damage			
Cervical	47(44.8%)	70(37.4%)	0.220
Lumbar	72(68.6%)	144(77%)	0.115
Laboratory data			
ESR titer (mm/h)	45.224±28.990	45.836±28.687	0.67
Accelerated ESR	88(83.8%)	154(82.4%)	0.751
CRP titer (mg/l)	19.322±25.402	19.920±21.681	0.317
Positive CRP	49(46.7%)	118(63.1%)	**0.006**
HLAB27	78(74.3%)	129(69%)	0.339
Tobacco	8(7.6%)	20(10.7%)	0.392
Radiologic joint damage			
Knees	21(20%)	18(9.6%)	**0.012**

Hips	44(41.9%)	48(25.7%)	**0.004**
Disease activity indices			
BASDAI	3.071±1.867	2.872±1.929	0.935
ASDASCRP	2.770±1.246	2.552±1.330	0.083
Disease activity			
Inactive	21(20%)	44(23.5%)	
Moderate	17(16.2%)	45(24.1%)	0.273
High	55(52.4%)	81(43.3%)	
Very high	12(11.4%)	17(9.1%)	

Table 2 : Treatment using by Ankylosing spondylitis patients

Characteristics (Mean±SD) or n(%)	With EAMs n=115	Without EAMs n=177	P value
Medical treatment			
Methotrexate	8(7.6%)	12(6.4%)	0.696
Sulfasalazine	80(76.2%)	155(82.9%)	0.166
NSAIDs	16(15.2%)	19(10.2%)	0.200
Biological treatment (Biotherapies)			
Humira	86(81.9%)	155(82.9%)	0.832
Remicade	7(6.7%)	17(9.1%)	0.469
Enbrel	9(8.6%)	12(6.4%)	0.494

Table 3: comparison between uveitis and psoriasis groups

Characteristics	AAU n=100		PsO n=15	
	Mean±SD or N(%)	P value	Mean±SD or N(%)	P value
Age	40.12±12.229	0.821	38.53±8.647	0.137
Sexe				
Males	50(50%)	0.073	13(76.5%)	**0.004**
Females	50(50%)		4(23.5%)	
Disease age onset	32.20±10.504	0.655	29.53±9.461	0.487
Disease duration	07.68±4.960	0.294	09.00±5.979	0.069
Duration morning stiffness	22.60±22.557	**0.044**	32.65±36.448	**0.032**
Spine damage				
Cervical	46(46%)	0.136	5(29.4%)	0.356
Lumbar	69(69%)	0.162	11(64.7%)	0.370
Laboratory data				
ESR titer (mm/h)	45.685±29.195	0.866	43.341±27.441	0.694
Accelerated ESR	84(84%)	0.713	14(82.4%)	0.953
CRP titer (mg/l)	19.194±25.698	0.325	27.193±24.507	0.215
Positive CRP	46(46%)	**0.005**	10(58.8%)	0.889
HLAB27	73(73%)	0.567	16(94.1%)	**0.030**
Tobacco	8(8%)	0.506	7(41.2%)	**<0.0001**
Radiologic joint damage				
Knees	19(19%)	**0.041**	7(41.2%)	**0.001**

Hips	43(43%)	**0.002**	9(52.9%)	0.050
Disease activity indices				
BASDAI	3.055±1.900	0.853	4.658±2.438	**0.011**
ASDASCRP	2.755±1.250	0.096	3.853±1.409	0.915
Disease activity				
Inactive	20(20%)		1(5.9%)	
Moderate	17(17%)	0.429	1(5.9%)	**<0.0001**
High	52(52%)		8(47.1%)	
Very high	11(11%)		7(41.2%)	
Medical treatment				
Methotrexate	7(7%)	0.941	1(5.9%)	0.871
Sulfasalazine	77(77%)	0.279	14(82.4%)	0.841
NSAIDs	15(15%)	0.253	2(11.8%)	0.977
Biological treatment				
Humira	82(82%)	0.862	15(88.2%)	0.523
Remicade	7(7%)	0.584	00(0%)	0.204
Enbrel	8(8%)	0.700	2(11.8%)	0.452