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ORIGINAL ARTICLE

Heart Involvement in a Moroccan Population with Spondyloarthritis: A Cross-sectional Study

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Abstract

Objectives: **The aim of this study was to investigate the prevalence of cardiac manifestations and their predictive factors in Moroccan patients with spondyloarthritis (SpA).**

Methods: **We have conducted a cross-sectional study over four months at the Department of Rheumatology in Mohammed VI University Hospital of Oujda, Morocco. All SpA patients fulfilled the 2009 Assessment SpondyloArthritis international Society (ASAS) criteria. Every patient had a cardiac check up including clinical examination, 12-lead electrocardiogram (ECG) and transthoracic echocardiography (TTE). Multiple logistic regression was used to analyze the associated factors with cardiac manifestations.**

Results: **We included 64 men and 30 women with a mean age of 37.32 ± 12.65 years old. The mean disease duration was 10.60 ± 7.61 years. Patients had a mean Ankylosing Spondylitis Disease Activity Score (ASDAS) CRP of 2.25 ± 1.38, a mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of 2.88 ± 2.26 and a mean Bath Ankylosing Spondylitis Functional Index (BASFI) of 33.52 ± 30.49. Traditional cardiovascular risk factors (CVRF) included dyslipidemia in 14.9%, hypertension in 9.6% and type 2 diabetes in 7.4% of the cases. Eight patients (8.5%) smoked and 3 patients (3.2%) used alcohol whereas 20 patients (21.3%) had a history of smoking and 5 patients (6.3%) a history of alcohol. Cardiac manifestations were found in 12 patients (13.3%): 3.3% had aortic regurgitation (AR), 1.1% had aortic dilatation, 1.1% had aortic valve thickening (AVT), 2.2% had mitral thickening, 1.1% had mitral regurgitation (MR), 1.1% had mitral stenosis (MS), 3.3 had pericarditis and 2.2% had complete right bundle branch block (RBBB). In multivariate analysis, cardiac involvement was significantly associated with extra-articular manifestations (OR = 6.05; 95% CI: 1.197-30.607, p = 0.029).**

Conclusion: **Based on these results, cardiac involvement was common and associated with the severity of the disease; hence, early detection of cardiac abnormalities and targeted treatment strategies of SpA and comorbidities are necessary to control the systemic inflammation and improve the excess of cardiovascular mortality in this group of patients.**

Keywords: Spondyloarthritis, Cardiac manifestations, Valvular heart disease, Prevalence

1. Introduction

Spondyloarthritis (SpA) is a heterogenic group of 5 immune-mediated inflammatory diseases: Ankylosing spondylitis (AS), Reactive arthritis (ReA), arthritis associated with inflammatory bowel disease (IBD), Psoriatic arthritis (PsA), and undifferentiated spondyloarthritis (uSpA) [1]. Its prevalence ranges widely from 0.03% in the Asia Pacific League of Associations for Rheumatology (APLAR) region to 2.5% in Alaska and Russia, depending on the genetic background, especially human leucocyte antigen B27 (HLA-B27) and geographic distribution of ethnic groups [2, 3]. If we consider SpA as a disease entity, the sex-ratio is nearly 1. It often affects young adults with a peak age of onset between 20 and 30 years old [1, 4].

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SpA is a complex polygenic disease; its pathogenesis remains a rheumatology enigma. It is triggered by environmental and genetic risk factors (HLA-B27, interleukin-23 (IL-23), endoplasmic reticulum aminopeptidase 1 (ERAP-1), microbiota changes and biomechanical stress) which lead to the activation of autoimmunity and chronic inflammation [1, 5, 6]. The mean SpA target is enthesis, but the synovial tissue can also be affected along with other extra-articular tissues such as the cardiovascular system [6, 7].

Cardiac involvement is a well recognized complication of SpA. It is common and associated with an increased mortality rate in this population when compared to the general population [6-10]. The spectrum of disease is large; it includes valvular heart disease (VHD), conduction disturbances and cardiomyopathy. These anomalies that are usually linked to comorbidities and treatments can also be induced by chronic inflammation [8, 11, 12].

If not treated, the chronic inflammation leads to fibrosis proliferation that affects the aortic root and valve, and could expand to the interventricular septum causing the dilatation of the aortic root, valve thickening and regurgitation. Occasionally, interventricular septum causes high-grade atrioventricular block (AVB) that represents the second highest prevalent cardiac manifestation after the AR in SpA patients [6, 7, 11, 13]. In 1930, the high prevalence of aortitis rates increasing among patients with SpA was described for the first time [14]. Quite recently, considerable attention is paid to the prevalence and prognostic value of VHD and the use of the pacemaker.

In this study, our purpose was to investigate the prevalence of cardiac manifestations and analyze their predictive factors in a Moroccan population of SpA patients.

2. Materials and methods

2.1. Study design

This cross-sectional study was carried out in the Rheumatology department of Mohamed VI University Hospital in Oujda, Morocco. Patients with spondyloarthritis (SpA) diagnosis visiting our care unit, from September 2017 to December 2017 were enrolled. We studied the cases of ninety-four patients. All patients fulfilled the 2009 Assessment SpondyloArthritis international society (ASAS) classification criteria for axial and peripheral SpA. Patients with history of infective endocarditis, neoplasm, or other chronic inflammatory rheumatism were excluded from the enrollment. Written informed consent was approved by the ethical committee and obtained from all subjects.

Abbreviation list

AR	Aortic regurgitation
AS	Ankylosing Spondylitis
AVB	Atrioventricular block
AVT	Aortic valve thickening
BBB	Bundle branch block
CRP	C-reactive protein
CVRF	Cardiovascular risk factors
ESR	Erythrocyte sedimentation rate
HLA	Human leucocyte antigen
MR	Mitral regurgitation
MS	Mitral stenosis
MVA	mitral valve area
SpA	Spondyloarthritis
VHD	Valvular heart disease

2.2. Data collection

Data-collection forms involved demographic data, age at disease onset, disease duration, history of peripheral joint surgery, clinical characteristics (axial involvement, peripheral arthritis, enthesitis), SpA-related comorbidities (psoriasis, uveitis, inflammatory bowel disease), disease severity reflected by the presence of axial involvement, coxitis, an anterior atlanto-axial subluxation, and extra-articular manifestations (EAMs) including pulmonary involvement, Sjogren syndrome, and renal amyloidosis. Traditional cardiovascular risk factors (CVRF) and history of cardiovascular disease (CVD) which is composed of ischemic heart disease, stroke and cerebrovascular disease were collected.

All participants underwent a rheumatological evaluation including swollen and tender joints counts and clinical enthesitis count. Pain intensity and fatigue were assessed by visual analog scale (VAS; 0-10). Anthropometric measurements and blood pressure were taken.

Every patient had a cardiac check up with research of clinical cardiac manifestations. A standard resting 12-lead ECG was recorded to analyze the rhythm and conduction disturbances (AVB of first to third degree, right bundle branch block (RBBB) or left bundle branch block (LBBB)). Transthoracic echocardiography (TTE) was performed for the diagnosis of cardiac abnormalities including those of the valve (regurgitation, thickening, stenosis, and dilatation) and pericardial effusion. Valve regurgitation and stenosis were assessed using semiquantitative methods to be categorized into

grade I (mild), grade II (moderate), and grade III (severe). Valve thickening was defined as focal or diffuse leaflet thickening superior to 2 mm for the aortic valve and 3 mm for the mitral valve. Ascending aorta dilatation was defined as >41 mm for the sinus or >35 mm for the annulus. Moreover, pericardial effusion was characterized as mild (<10 mm of echo-free space in diastole), moderate (10-20 mm), or large (>20 mm).

A blood sample with analysis including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), HLA-B27 status, and other standard hematological assessments were undertaken.

Disease activity was assessed with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; 1-10) and the Ankylosing Spondylitis Disease Activity Score based on CRP and ESR (ASDAS-CRP, ASDAS ESR). A BASDAI score $\geq$ of 4 on a 10-point scale was accepted to designate active disease. The ASDAS scores were used to classify disease activity as inactivity (<1.3), low (1.3-2.1), high (2.1-3.5) or very high (>3.5). Functional status was evaluated by the Bath Ankylosing Spondylitis Functional Index (BASFI; 1-100).

2.3. Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics version 20 software. Descriptive statistics encompass numbers (percentages) for categorical variables and means (standard deviation) or medians for continuous variables. Chi-square test or Fisher's exact test were used to compare qualitative variables and the Student's t-test was performed for quantitative variables. A multivariate logistic regression analysis was performed to determine the predictive factors of cardiac manifestations. The level of significance was accepted as p value < 0.05.

3. Results

The socio-demographic and clinical characteristics of the study population are shown in Table 1. Cardiac manifestations were found in 12 patients (13.3%) in which 3.3% had aortic regurgitation (AR) (Fig. 1). Grade 1 AR and grade 2 AR were observed in 2 patients and one other patient respectively. 1.1% of the population had ascending aortic dilatation (47 mm) and 1.1% had aortic valve thickening (AVT). Mitral thickening was seen in 2.2% in which one patient had a focal thickening with mitral valve area (MVA) measured by pressure half-time of 5.2 cm^2 and a peak gradient of 3.2 mmHg. Furthermore, 1.1% of the patients had mitral regurgitation (MR) classified as mild in grading mitral regurgitation severity, and 1.1% had mitral stenosis (MS) (the MVA measured by planimetry and doppler was >1.5 cm^2) (Fig. 2). 3.3% of the population had pericarditis in which one patient had moderate pericardial effusion (Fig. 3) and two had mild disease. Additionally, 2.2% of the population had complete right bundle branch block (RBBB).

In comparison with the group without cardiac involvement (Table 2), the presence of cardiac abnormalities was significantly associated with severe SpA: EAMs (p = 0.04), an anterior atlanto-axial

Table 1. Clinical data in 94 patients with SpA.

Clinicopathological and therapeutic patterns	
Demographic characteristics	
Sex (F/M) (number, %)	30(31.9)/64(68.1)
Age, years (mean, SD)	37.32 ± 12.65
SpA characteristics	
Disease duration, years (mean, SD)	10.60 ± 7.61
Axial involvement (number, %)	71 (75.5)
Peripheral arthritis (number, %)	41 (43.6)
Enthesitis (number, %)	69 (73.4)
EAMs (number, %)	49 (52.1)
Uveitis (number, %)	13 (13.8)
Psoriasis (number, %)	14 (14.9)
IBD (number, %)	11/17 (11.7)
Coxitis (number, %)	39 (42.9)
aAAS (number, %)	2 (2.1)
CRP, mg/l (median, range)	8.5 (0-197)
ESR, mm/h (median, range)	16 (1-131)
BASDAI (0-10) (mean, SD)	2.88 ± 2.26
ASDAS CRP (mean, SD)	2.25 ± 1.38
ASDAS VS (mean, SD)	2.19 ± 1.23
BASFI (0-100) (mean, SD)	33.52 ± 30.49
Traditional CVRF (number, %)	
Hypertension (SBP≥140 and/or DBP≥ 90 and/or antihypertensive drugs)	9 (9.6)
Diabetes type 2	7 (7.4)
Dyslipidemia	14 (14.9)
Obesity (>30 BMI)	11 (11.7)
Current smoking	8 (8.5)
Past smoking	20 (21.3)
Current alcohol consumption	3 (3.2)
Past alcohol consumption	5 (5.3)
History of CVD (number, %)	0 (0.0)
Cardiac manifestations (number, %)	12 (13.3)
SpA-related medications (number, %)	
DMARDs	
TNF inhibitors	36 (38.3)
Methotrexate	30 (31.9)
Sulfasalazine	23 (24.5)
Non steroidal anti-inflammatory drugs	45 (47.9)

aAAS: anterior atlanto-axial subluxation, ASDAS: Ankylosing Spondylitis Disease Activity Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, CVD: cardiovascular disease, CVRF: cardiovascular risk factors, DMARDs: Disease-modifying antirheumatic drugs, EAMs: extra-articular manifestations, ESR: erythrocyte sedimentation rate, IBD: inflammatory bowel disease, SD: standard deviation.

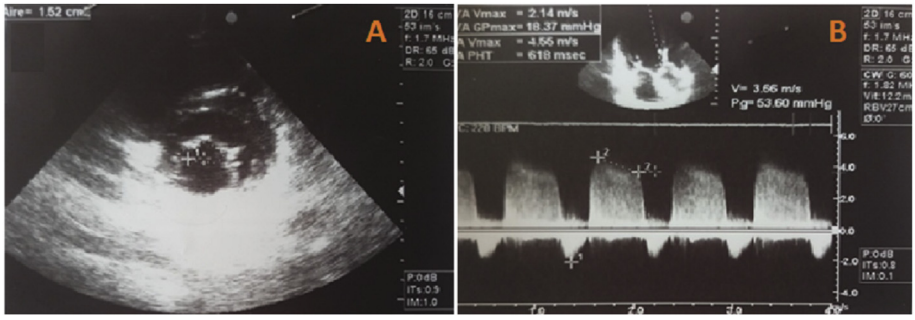

Fig. 1. Transthoracic echocardiography of a 37-years-old woman with severe spondyloarthritis. (A) The parasternal short-axis view demonstrating a mitral stenosis (mitral valve areas > 1.5 cm^2). (B) A four-chamber view revealing aortic regurgitation (peak gradient = 53.60 mmHg).

subluxation (p = 0.01) and axial involvement (p = 0.037). Concerning the type of cardiac manifestations, patients with VHD had longer disease duration (12.00 ± 8.71 years) compared to those without VHD; however, this difference was not statistically significant. EAMs were frequent among the group with cardiac involvement, but only VHD was significantly associated with EAMs (p = 0.008). Patients with pericarditis and conduction disorders had higher disease activity and statistically significantly higher ESR (p = 0.004). Moreover, no significant association between conventional CVRF and cardiac involvement was found. In multivariate analysis, cardiac involvement was the only predictive factor of EAMs (OR = 6.05; 95% CI: 1.197-30.607, p = 0.029).

4. Discussion

In the present study, the pooled prevalence of cardiac manifestations reached 13.3%. The most common abnormality was VHD (7.8%) followed by pericarditis (3.3%) and conduction defects (2.2%). This was within the range described in former studies; it widely ranged from 2% [15, 16] to 14% [18] and it can reach up to 82% [18, 19] when compared with the normal population. Kinsella et al. [17] noted that 14% of 97 patients with AS had cardiovascular anomalies. Another contemporary study by Sukenik et al. [20] showed that 42.5% of 40 patients with AS had cardiac manifestations. However, the results of other studies are still conflicting. In fact, a recent study by Sorouch et al. [21] demonstrated that patients having AS does not influence heart involvement.

The most commonly recognized cardiac manifestation of SpA is aortic valve disease, which is usually restricted to the ascending aorta and aortic arch, and includes aortic regurgitation (AR), aortic valve thickening (AVT) and aortitis [6]. Its prevalence increases with age and is especially related to the disease duration [22-24]. In our study, the prevalence of aortic involvements was distributed as follows: 3 (3.3%) had AR, 1 (1.1%) had aortic dilatation and 1 (1.1%) had AVT. These results were in

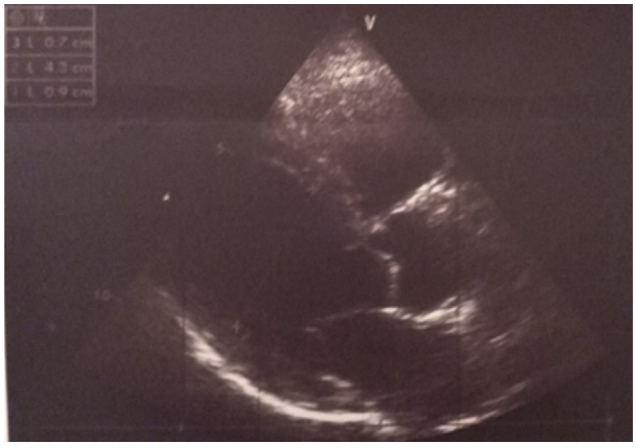

Fig. 2. The transthoracic echocardiography (parasternal long-axis view) of a 62-years-old woman with psoriatic arthritis revealing mild thickened aortic and mitral valve.

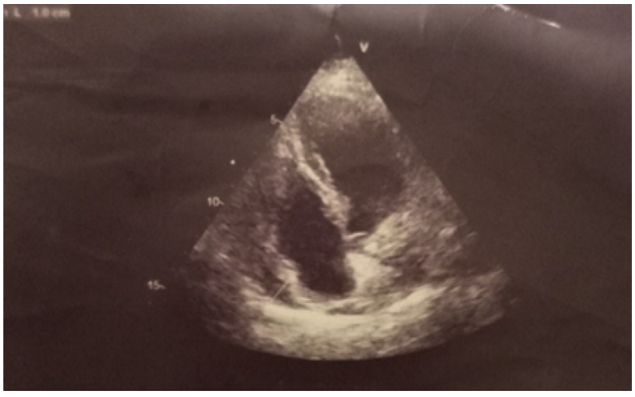

Fig. 3. The transthoracic echocardiography (in the apical four-chamber view) of a 38-years-old woman with spondyloarthritis revealing echo-free space of 10 mm located laterally to the right atrium, suggestive of moderate pericardial effusion.

Table 2. Comparison between SpA patients with and without cardiac manifestations.

	Patients with cardiac involvement (n = 12)	Patients without cardiac involvement (n = 82)	*p* value
SpA characteristics			
Disease duration, years (mean, SD)	11.50 ± 7.14	10.52 ± 7.79	0.68
Axial involvement (number, %)	6 (50)	61 (78.2)	0.037
aAAS (number, %)	1 (8.3)	0 (0.0)	0.01
Coxitis (number, %)	3 (30)	34 (44.2)	0.39
Extra-articular manifestations (number, %)	4 (33.3)	9 (11.5)	0.04
Comorbidities (psoriasis and others) (number, %)	10 (83.3)	37 (47.4)	0.02
CRP, mg/l (median, range)	6.5 (0-110)	8.5 (0-197)	0.57
ESR, mm/h (median, range)	35 (1-131)	16 (1-124)	<0.001
Traditional CVRF (number, %)			
Hypertension (SBP≥140 and/or DBP≥ 90 and/or antihypertensive drugs)	3 (25)	6 (7.7)	0.06
Diabetes type 2	2 (16.7)	5 (6.4)	0.21
Dyslipidemia	3 (25)	11 (14.1)	0.33
Obesity (>30BMI)	0 (0.0)	11 (14.1)	0.16
Current smoking	0 (0.0)	8 (10.3)	0.24
Current alcohol consumption	0 (0.0)	2 (2.6)	0.57

aAAS: anterior atlanto-axial subluxation, CRP: C-reactive protein, CVRF: cardiovascular risk factors, ESR: erythrocyte sedimentation rate, SD: standard deviation.

agreement with previous studies which demonstrated an increased prevalence of SpA-related AR, from 1.7% in a study by Bernstein et al. in 1951 to 10% in an echocardiography survey of 24 AS patients conducted by Graham et al. in 1958 [16, 17]. The average rate of AR in longstanding AS was 6.9% between 1970 and 1983 and increased to 10.8% (going from 1.8 to 16%) in the reviewed literature from 1987 to 2005. This finding was explained by the continuous sensitivity and specificity enhancement of cardiology techniques [18, 25, 26]. In a cohort of 42 327 age-matched patients, the prevalence of aortic and mitral valve diseases increased from less than 4% in those aged 65 to 69 years old to 20% in those aged 80 years old or older when compared with patients without SpA [19]. This study also reported that the prevalence of aortic valve surgeries was slightly higher within this population group compared with the control group [19]. Bengtsson et al. reported in their cohort 1.2% of AR among a population where only 27% were older than 60 years [27]. The results showed that the patients' age influenced the results since these affections are usually rare among the young population, while being very common among elderly patients. In early AS, a 4% prevalence of aortic disease has been reported [28].

Mitral valve disease is known to occur among SpA patients but remains less common than aortic valve disease; its manifestations can go from thickening to the severe regurgitation needing valve replacement. Its prevalence in SpA patients increases with age like the prevalence of aortic valve disease [16, 19]. In our study, 2.2% of patients had mitral thickening, 1.1% patients had mitral regurgitation (MR) and 1.1% had mitral stenosis (MS). Based on the findings in literature, mitral valve disease is more prevalent in longstanding AS (going from 32 to 40%) [18, 25]. In a study of homogeneous population of 100 male AS patients, the prevalence of MR was 29% [24, 25]. In 2018, in comparison with patients without SpA, Ward et al. found in their cohort a slightly higher risk of mitral valve disease in all groups of age [19]. In case series, echocardiographic evidence of MR was described to go from 5% to 74% [18, 19, 24, 26].

Conduction disorders as bundle-branch blocks (BBB), atrioventricular blocks (AVB), and intraventricular blocks have been frequently observed in patients with SpA, especially among those with associated valvular involvement and may require a pacemaker [19, 29-31]. In the present study, only two patients (2.2%) had RBBB. Similarly, the prevalence in former studies varied from 1.1% [32, 33] to 33% [34, 35]. It was previously reported that the rates of conduction disturbances varied according to the disease duration but occurred among all ages [23, 28, 29, 32]. Moreover, it was mentioned that HLA-B27 was strongly associated with conduction disturbances even in the absence of SpA and higher disease activity [16, 29, 36].

Myocardial dysfunction and pericarditis can occur among SpA patients but remain uncommon [15, 32, 37-39]. In our study, 3.3% of our patients had pericarditis whereas prevalence rates reported in former studies were lower [31].

Multivariate logistic regression analysis identified SpA-related EAMs as an independent predictive factor for the development of cardiac involvement

(OR = 6.05; 95% CI: 1.197-30.607, p = 0.029). This could provide an insight on how the severity of SpA could contribute to the development of cardiac manifestations and prompt us to elaborate an optimal management of SpA and its EAMs. In several studies, age and disease duration were associated with cardiac manifestations [24, 26]. Furthermore, the presence of peripheral arthritis (other than hip and shoulder involvement) increased the risk for cardiac abnormalities [17, 29]. No significant difference was found between the last cited parameters and the cardiac involvement in our study.

In this cross-sectional study, there was no association between SpA treatment and heart involvement. This aspect could make the subject of a future prospective study.

5. Conclusion

SpA and its EAMs increase the risk of cardiac involvement. This must motivate clinical awareness and needs a tight collaboration between rheumatologists and cardiologists to elaborate targeted screening approaches for this risk group. Indeed, an early diagnosis, the determination of the early therapeutic response and its monitoring have become more and more important due to the availability of effective therapies, especially biotherapies.

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Disclosures of interest

None declared.

Authors contribution

Jalila Eddarami: Conception and design of Study, Literature review, Acquisition of data, Analysis and interpretation of data, Research investigation and analysis, Data collection, Drafting of manuscript, Data preparation and presentation, Revising and editing the manuscript critically for important intellectual contents; **Hamida Azzouzi:** Acquisition of data, Analysis and interpretation of data, Research investigation and analysis, Revising and editing the manuscript critically for important intellectual contents; **Linda Ichchou:** Conception and design of Study, Acquisition of data, Analysis and interpretation of data, Research investigation and analysis, Revising and editing the manuscript critically for important intellectual contents, Supervision of the research, Research coordination and management.

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