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Systemic Lupus Erythematosus: Female Versus Male

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Abstract **Original Research Article**

Introduction: Systemic lupus erythematosus (SLE) is an autoimmune disease, uncommon in men. The study of gender differences in SLE has been the subject of several publications. The main aim of our study is to identify gender differences in terms of clinical manifestations, immunological profile, activity score, and disease evolution in our Moroccan population. ***Results:*** We analyzed 279 patients (21 men versus 258 women), with a mean age at diagnosis of 37.54 +/- 23.39 years for women and 42.74 +/- 16.33 years for men. A comparison of clinical and immunological manifestations showed that male patients had a higher prevalence of renal involvement, lymphopenia, leukopenia, and general signs, but the difference was not significant. However, we did establish a significant correlation between male sex and cardiac involvement (P=0.013) as well as neuropsychiatric involvement (P=0.05). We also observed a significant association with anti-SSA antibodies (p=0.007). Dermatological and articular events were more frequent in women than in men, with a statistically significant association between female gender and photosensitivity (p=0.037). There was also a statistically significant correlation between women with RNP antibodies (p = 0.016) and anti-native DNA antibodies (p=0.047). The outcome was good in 67% of men (vs. 86.2% p=0.802), with response to treatment and control of the disease, and poor in 33% of men (vs. 13.9% %, p=0.019). ***Conclusions:*** Our study reveals the influence of gender on certain clinical manifestations of SLE. Dermatological and articular manifestations are more frequent in women, whereas men present a more severe disease, with a higher frequency of renal, cardiac, and neurological involvement.

Keywords: Systemic lupus erythematosus, clinical manifestations, gender, men.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the presence of autoantibodies with multi-systemic damage. It is uncommon in men, with a female-to-male sex ratio of 9. Differences in the clinical presentation and severity of SLE in men and women are increasingly reported in the literature [1, 2]. However, conclusions are often incoherent due to differences between studies in terms of ethnicity, date of disease onset, duration of follow-up, and sample size. Based on these data, the main objective of our study is to elucidate gender differences in clinical manifestations, immunological profile, activity score, and disease course in our Moroccan population.

MATERIAL AND METHODS

Type and duration of study

This was a longitudinal study conducted in the internal medicine and onco-hematology department of the Hassan II University Hospital in Fez, covering an 8-year period between January 2012 and December 2020.

Patients Studied

We analyzed 279 patients with systemic lupus erythematosus diagnosed and treated in the internal medicine and onco-hematology department. The diagnosis was made according to the EULAR /ACR 2019 and SLICC classification criteria.

Data Analysis

An evaluation form was used to collect data from the files.

Statistical analysis was carried out in collaboration with the Laboratory of Epidemiology, Clinical Research, and Community Health at the Faculty of Medicine and Pharmacy in Fez. Descriptive statistics were used to summarize patient characteristics, including age, sex, medical history, duration of illness, manifestations of SLE, disease activity score, treatment received, and disease course. Frequency was used to account for qualitative variables,

while mean and standard deviation were used to represent quantitative variables.

Comparison of different systemic and immunological impairments in lupus patients by gender was performed, using Student's t-test to compare means and chi-square or Fisher's exact test to compare percentages.

Univariate analysis and logistic regression were used to search for correlations between the two sexes for the different systemic and immunological impairments in lupus patients. The significance threshold was set at 0.05.

RESULTS

Twenty-one men were identified among 279 SLE patients. The female/male sex ratio was 12.28. The age of diagnosis for women was 37.54 +/- 23.39 years (16-75 years), while men were diagnosed at 42.74 +/- 16.33 years (16-70 years). Skin manifestations were present in 57% of men (vs. 75% of women, p= 0.07): photosensitivity in 47.6% of men (vs. 69.6% of women, p=0.037), Vespertilio erythema in 47.6% of cases (vs. 56.8%, p=0.415). Men had arthralgia in 66.6% (vs. 80.6%, p= 0.159) and arthritis in 38%. Two cases of Raynaud's phenomenon (vs. 10% of women, p=1). Respiratory and cardiac manifestations were present in 23.8% of men (vs. 22.1%, p=1) and 57.1% of men (vs. 30.58%, p=0.013) respectively. Renal involvement was observed in 52.38% of men (vs. 38.37%, p= 0.212), with no cases of chronic renal failure in men (vs. 5% of women). Neuropsychiatric manifestations were present in 42.8% of men (vs. 24% of women, p= 0.05).

Concerning hematological involvement, anemia was observed in 52% of men (vs. 47.7%, p= 0.769), and in only one case it was autoimmune and hemolytic (vs. 6.4% of women, p=0.791). Thrombocytopenia occurred in 19% of patients (vs 19.7%, p=0.936). Leukopenia and lymphopenia were noted respectively in 28.5% of men (vs 19.3%, p=0.392), and 57% of men (vs 54.6%, p= 0.825).

The immunological tests revealed antinuclear antibody positivity in all our patients, anti-native DNA antibodies in 47.6% of men (vs. 70.9% of women, p=0. 047), anti-SM, anti-RNP, and anti-SSA antibodies were present in 38.8% of men (vs 26.7%, p=0.281), 33% of patients (vs 12.7%, p= 0.016) and 23.8% of patients (vs 27.5%, p=0.007) respectively. Anti-phospholipid antibodies were detected in 14.2% of men (vs 12.4%, p=0.802).

All our patients were treated with a synthetic antimalarial, and corticosteroids were prescribed in 72% of cases, with immunosuppressive therapy as follows: methotrexate in 10%, cyclophosphamide, and azathioprine in 31% and 20% respectively. Rituximab was used in 5.3% of patients, and MMF in 6%.

Progression was favorable in 67% of men (vs. 86.2%, p = 0.802), with response to treatment and control of disease, poor in 33% of men (vs. 13.9%, p = 0.019).

The aim of our analytical study was to investigate correlations between the two sexes for the various systemic and immunological impairments in lupus patients. Table (1) illustrates the different associations found in our population. We found a significant correlation between male sex and age over 45 (p= 0.027), as well as between cardiac (p=0.013) and neuropsychiatric (P=0.05) disorders. Other manifestations were more frequently observed in men, such as renal impairment, lymphopenia, leukopenia, and general signs, but the difference was not significant. Immunologically, there was a significant association with anti-RNP antibody (p = 0.016).

We also report a statistically significant association between female gender and photosensitivity (p = 0.037), while no other significant correlation was identified for the rest of the clinical manifestations. Immunologically, there was a statistically significant correlation between anti-SSA antibodies (p=0.007) and anti-native DNA antibodies (p=0.047). No correlation was detected with anti-phospholipid antibodies.

Table 1: Correlations between the sexes for the various systemic and immunological disorders in our population, Results are presented as number (%) of patients

	Female N= 258	**Male N=21**	**p**
Age > 45 years	64(24)	11(52,3)	0,027
Fever	56(21,7)	7(33,3)	0.227
Photosensitivity	179(69,3)	10(47,6)	0.037
Lupus discoidus	32(12,4)	1(4,7)	0.486
Erythema vespertilio	149(57,7)	10(47,6)	0.415
Alopecia	59(22,8)	3(14,2)	0.430
Arthralgia	208(80,6)	14(66,6)	0.159
Arthritis	95(36,8)	8(38)	0.907
Raynaud syndrome	28(10,8)	2(9,5)	1
Thrombotic manifestations	11(4,2)	0(0)	0.333
Kidney damage	99(38,3)	11(52,3)	0.212

	Female N= 258	**Male N=21**	**p**
Cardiac involvement	78(30,2)	12(57,1)	0.013
Pleuropulmonary involvement	57(22)	5(23,8)	1
Neuropsychiatric involvement	62(24)	9(42,8)	0.05
Digestive disorders	17(6,5)	2(9,5)	0.634
SLEDAI activity score at diagnosis	70(27,1)	10(47,6)	0.001
Hemolytic anemia	16(6,2)	1(4,7)	1
Leukopenia	50(19,3)	6(28,5)	0.312
Thrombocytopenia	51(19,7)	4(19)	1
Anti-native DNA	183(70,9)	10(47,6)	0.047
Anti-Sm	64(24,8)	7(33,3)	0.281
Anti- SSA	71(27,5)	5(23,8)	0.007
Anti-RNP	33 (12,8)	7(33,3)	0.016
Anti-phospholipid Ac	31(12)	3(14,2)	0.802

DISCUSSION

SLE is a pathology of young women and rarely affects men. In our series, 21 of 279 (7.5%) SLE patients were men. This frequency is similar to that observed in South Korea [3] and Tunisia [4], although it remains higher in other studies [5-7].

The mean age of diagnosis in our study is higher in men (42.47 years) than in women (37.54 years). This is comparable with a Swedish study [8], in contrast to the cohort of Garcia MA *et al.*, where the age of men at diagnosis is much younger, with a median age of 29.2 years [9], probably due to the delayed diagnosis and atypical male presentation in our population.

Female predominance is classic, with a female-to-male sex ratio of 11.5 in South Korea and Tunisia, 8.5 in Saudi Arabia [10], 8.7 in China [11] and 12.28 in our study.

The differences in clinical and immunological manifestations between the sexes during the course of SLE have been the subject of several studies [1, 12, 13, 2] in which women and men present distinct characteristics Table 2.

In our series, dermatological and articular manifestations were more frequent in women than in men, in agreement with the results of other studies [1, 7]. On the other hand, we noted a similar frequency of arthritis in our patients, in accordance with what has been reported in previously cited studies. In contrast, a Taiwanese study found a lower frequency of arthritis in males [14].

Several studies have shown that renal involvement is more frequent in men than in women with lupus [15-17]. Some of these have found a greater susceptibility to progression to end-stage renal disease (ESRD) [18]. In our series, we also note a higher frequency of renal involvement in men, without progression to renal failure, but no significant association has been proven. This inconsistency could possibly be explained by our small sample size and patient selection bias. These studies have shown that the higher risk of ESRD in lupus men could be explained by hypertension, atherosclerosis, smoking, or hyperlipidemia. All these factors have a negative impact on the progression of kidney disease.

An American study found that leukopenia, lymphopenia, and thrombocytopenia were about three times more frequent in men than in women [19]; unlike our population, where the frequency was similar in both sexes, except for lymphopenia, which was more frequent in men.

Neuropsychiatric involvement was twice as frequent in lupus-affected men as in women; this difference varied from study to study; it was more frequent in Ward's series [20] and less frequent for other authors [5, 8].

Cardiac involvement was significantly more frequent in men, although this was not evident in the cohorts of Faezi *et al*., Stefanidou, and Kok [3].

We were also able to demonstrate a clear trend towards increased mortality in men with SLE compared with women, with a statistically significant association. This finding has been supported by several previously cited studies, several theories of which have been proposed to explain the dismal prognosis in lupus-affected men: delayed diagnosis, atypical clinical presentation, as well as poor compliance with treatment in men.

It is important to note that the results observed in our study are specific to the sample studied from our Moroccan population and cannot necessarily be generalized to other populations. Furthermore, these results should be interpreted with caution and considered as associations and not as evidence of causality. Further studies are required.

Table 2: Comparison of clinical, hematological, and immunological manifestations between the sexes during SLE according to studies

	Ramirez Sepulveda 2019			**Faezi *et al.*, 2014**			**Tan *et al.*, 2012**			**Stefanidou2011**			**Our study**		
	F 1060	M 65	P	F 2116	M 239	P	F 1822	M 157	P	F 535	M 59	P	F 258	M 21	P
Fever (%)	-	-	-				-	-	-	26.9	32.2	NS	21,7	33,3	0,227
Photosensitivity (%)	66.7	43.4	0.0001	57.8	51.5	0.063	55.5	40.4	0.0002	31.6	13.6	0.004	69,3	47,6	0,037
Lupus discoidus (%)	24	18.7	0.13	13	25.9	0.000	19.8	24.7	0.133	5.8	11.9	NS	12,4	4,7	0,486
Erythema vespertilio (%)	55.8	39.2	0.0001	-	-	-	52.4	39.7	0.01	19.8	13.6	NS	57,7	47,6	0.415
Alopecia (%)	-	-	-				56.3	28.2	0.0001	-	-	-	22,8	14,2	0.430
Arthralgia (%)	-	-	-				92.7	87.9	0.018	63.2	45.8	0.004	80,6	66,6	0,159
Arthritis (%)	79.2	69.9	0.007	71.7	61.1	0.01	74.4	70.3	0.326	43.9	35.6	NS	36,8	38	0,907
Raynaud syndrome (%)	-	-	-	-	-	-	-	-	-	24.1	11.9	NS	10,6	9,5	1
Thrombotic manifestations (%)	29.9	54.2	0.0001	2.8	2.4	0.718	-	-	-	16.1	27.1	0.002	4,2	0	0,333
Kidney damage (%)	-	-	-	0.4	1.4	0.09	-	-	-	9.5	13.6	NS	38,3	52,3	0.212
Cardiac involvement (%)	36.2	47.1	0.02	15.6	18.4	0.268	44.7	41.7	0.526	9.5	13.6	NS	30,2	57,1	0,013
Pleuropulmonary involvement (%)	-	-	-	-	-	-	13.3	19.9	0.0103	4.7	20.3	0.001	22	23,8	1
Neuropsychiatric involvement (%)	9.1	11.4	0.35	3.6	2.4	0.358	-	-	-	18.3	20.3	NS	24	42,8	0,05
Digestive disorders (%)	-	-	-				-	-	-	9.2	16.9	0.039	6,5	9,5	0,634
Hemolytic anemia (%)	7.2	5.5	0.48	4.3	2.9	0.314	10.1	12.8	0.19	-	-	-	6,2	4,3	1

	Ramirez Sepulveda 2019			**Faezi *et al.*, 2014**			**Tan *et al.*, 2012**			**Stefanidou2011**			**Our study**		
	F 1060	M 65	P	F 2116	M 239	P	F 1822	M 157	P	F 535	M 59	P	F 258	M 21	P
Leukopenia (%)	42.7	40.2	0.58	35.8	28.5	0.024	43.3	47.4	0.105	-	-	-	19,3	28,5	0,312
Thrombocytopenia (%)	35.6	32.3	0.47	17.7	19.2	0.547	19.5	28.8	0.001	-	-	-	19,7	19	1
Anti-native DNA (%)	59.5	66.1	0.15	71.3	67.8	0.254	61.7	68.2	0.02	-	-	-	70,9	47,6	0.047
Anti-SM (%)	14	15	0.76	-	-	-	17.5	23.5	0.006	-	-	-	24,8	33,3	0,281
Anti- SSA (%)	-	-	-	-	-	-	29.9	23.9	0.17	-	-	-	27,5	23,8	0,007
Anti-RNP (%)	-	-	-	-	-	-	26.4	29.7	0.09	-	-	-	12,8	33,3	0,016

CONCLUSION

Our study shows the influence of gender on some clinical manifestations of SLE. Men are more likely to suffer from more severe forms of the disease, both renal and extra-renal. In addition, they often have a late onset and a poor prognosis. However, the high frequency of renal involvement in men does not appear to be responsible for the increased mortality observed. This category requires enhanced awareness and vigilance in clinical practice.

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