Systemic Lupus Erythematosus in Algerian Men: Clinical-Biological and Evolutionary Analysis of 19 Algerian Men

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ABSTRACT

Objectives: the aim of our study was to precise the epidemiological, clinicobiological, immunological, and evolutionary profile of systemic lupus erythematosus in Algerian men.

Methods: A retrospective multicenter study was carried out on 19 Algerian male lupus patients, diagnosed according to the ACR and SLICC criteria and followed between 2006 and 2019 on a total of 203 cases of systemic lupus erythematosus in western Algeria.

Results: 203 SLE patients were included, 19 men (9.4%) and 184 women (90.6%) with F/ M sex ratio of 9.68 / 1. The mean age at diagnosis was 33 ± 9.49 years. The most frequent clinical manifestations were joint involvement (84.2%), cutaneous (68.4%) and hematological dysfunction (63.2%). 15.8% had lupus nephropathies with the predominance of class IV; Raynaud’s syndrome and neuropsychiatric involvement were found in 26.3%. Comparison of these results with those of 184 lupus women showed a significant frequency of mucosal ulcer (p=0.00011) and neuropsychiatric damage in men (p=0.011), while alopecia in women (p=0.021). As well, hypocomplementemia (p=0.0004), anti Sm antibodies (p=0.0053) and anti Ribo some (p=0.028) were more frequent in men; while anti-SSA (p=0.003) and anti-SSB (p=0.011) antibodies were more frequent in women. Survival of lupus men was equal to 100% throughout the studied period.

Conclusion: Male lupus is rare. The Algerian man suffers from SLE in a less severe form compared to other data in the literature, which is manifested by a lower frequency of organ damage and mortality.

Keywords: Male lupus, epidemiology, clinical polymorphism, evolutionary profile, western Algeria.

1. INTRODUCTION:

Systemic lupus erythematosus (SLE) is an organ-specific autoimmune disease of unknown and possibly heterogeneous etiology. It is associated with high clinical polymorphism and characterized by multifactorial dysfunction of the immune system with the production of a wide variety of autoantibodies directed primarily against nuclear antigens. The disease preferentially affects women of childbearing age but more rarely males. The clinical, biological and progressive features of lupus in men vary from one study to another.

In order to contribute to the precision of the epidemiological, clinical, biological, immunological and evolutionary profile of SLE in the Algerian population, we carried out a first multicentric study on Algerian male patients with SLE.

2. MATERIAL AND METHOD:

This is a retrospective multicenter study of 19 male lupus patients, diagnosed and followed between January 2006 to December 2019 in the University Hospital of ORAN (EHUO) and the ABDELKADER HASSANI University Hospital of Sidi Bel Abbes (CHU-SBA) West of Algeria. All patients are Algerians, adults, and met the lupus criteria of the ACR 1997
and SLICC of 2012 \textsuperscript{5}. Patients under the age of 16 were excluded because they were followed by a different medical team (pediatrics). One hundred and eighty-four (184) female lupus diagnosed during the same period, in the same hospitals above-mentioned, were used as a control population to compare the clinic-biological and immunological manifestations and evolution between the two sexes.

The standardized data collection included demographic, clinical, laboratory data, 2002 SLICC criteria and 1997 ACR criteria \textsuperscript{6}, therapeutic interventions and iatrogenic complications. Information on deaths during hospitalization was collected from hospital records and death registers. Noted that all recorded deaths were female, ethnicity could not be determined since Algerians are generally descended from either Berbers or Arabs, which are the two predominant ethnicities in Algeria. For associated autoimmune diseases, the definition criteria were specific to each disease: American-European criteria for Gougerot-Sjögren syndrome \textsuperscript{7}, Sydney international criteria for SjP \textsuperscript{8}, joint ACR / EULAR criteria for Rheumatoid Arthritis \textsuperscript{9}.

Our patients were divided into two groups according to sex (Male and Female), whose studied parameters and qualitative variables were expressed in numbers and percentages, the quantitative variables on average with their standard deviations and / or 95% confidence interval calculated according to the normal distribution. In the case of non-normal distribution, the quantitative variables were described with the median. The Chi\textsuperscript{2} test of Person with Fisher correction was used for the comparison of the numbers. Significance was retained for values of $p \leq 0.05$.

### 3. RESULTS:

Nineteen male lupus, or 9.4%, all white, meeting the criteria of the ACR, were collected during a period of 13 years out of a total of 203 systemic lupus with a percentage equal to 90.6% of female lupus, which gave a female / male sex ratio of 9.68 / 1. The mean age at diagnosis was 33 years ± 9.89 (range: 18 and 51 years), identical to that of the female group 29.11 years ± 13.84. The mean duration of patient follow-up was 12.3 years. A family history of autoimmune disease in the first degree was found in 17 patients (89.5%), it was familial lupus in 3 cases (15.8%), diabetes in 3 cases (15.8%), Arterial hypertension (hypertension ) in 04 cases (21.1%), diabetes + HTA in 03 cases (15.8%), and 04 patients (21.1%) had familial TCDS from other AI diseases (Rheumatoid Arthritis, Thyroid, Psoriasis, Vitiligo).

A triggering factor was noted in 08 patients (42.10%) (viral infection of the CMV and EBV type in 02 cases, sun exposure in 04 cases and 02 cases by psychological stress due to the death of one of the relatives). No case of induced lupus has been observed.

The frequency of clinicobiological and immunological manifestations were shown in Tables 1 and 2. Joint involvement represented the most dominant clinical manifestation (84.2%) comprising polyarthritis in 10 cases and non-erosive arthritis in 06 cases, followed by cutaneous manifestations with a percentage equal to 68.3% (photosensitivity, malar rash, oral ulcerations in 10 cases, i.e. 52.6%), Raynaud syndrome (26.3%), neuropsychiatric involvement noted in 26.3%, pulmonary involvement (15.8%), pericarditis found in only one case (5.3%). Gastrointestinal manifestations were rare, only one patient has gastrointestinal bleeding.

Class IV lupus nephropathy found in 02 cases and only one case with end-stage renal failure requiring the use of hemodialysis.

Haematological involvement was very common with a percentage equal to 63.2% of cases. The anemia observed in 47.4% of cases was autoimmune hemolytic (AHA) in 15.3% of cases. Six patients developed Leukopenia (31.6%), five patients had Lymphopenia (26.3%), Thrombocytopenia in 07 cases (36.8%) and neutropenia in only one case.

Regarding serological tests, all patients presented positive ANA (100%). The speckled appearance (57.8%) and the homogeneous appearance (31.5%) were the most common appearances. The mixed homogeneous + speckled appearance was rare (10.5%). Anti-native DNA antibodies were present in 68.4% of patients, anti-Sm in 47.4%, anti-RNP in 31.6%. Anti-SSA antibodies found in 26.3% of patients, anti-Ribosome in 02 cases (10.5%). The anti-nucleosyme, anti-centromere and anti-Scl-70 antibodies were each noted in a single case (5.3%). No case of antiphospholipid syndrome has been observed. Hyppocomplementemia was observed in nine cases (47.4%).

The inflammatory syndrome was very remarkable in our patients, the sedimentation rate (SV) was accelerated in 89.4% of patients, with an average of the SV (1st hour) equal to 56.84 ± 37.35 mm / h and SV (2nd hour) equal to 86.22 ± 38.33 mm / h. C reactive protein (CRP) was positive in 73.6% of cases with a mean equal to 18.10 ± 24.61 .

The comparison of male and female lupus (Tables 1 and 2) showed a significant increase in the frequency of oral and nasal ulcerations ($p = 0.000011$) in men, neuropsychiatric damage ($p = 0.011$) in men and non-scarring alopecia ($p = 0.021$) in women.

Other manifestations were seen more frequently in men, but the difference was not significant. These were general signs such as: fever (21.1% vs 9.2%), asthenia (57.9% vs 39.1%), weight loss (15.8% vs 19%) and anorexia (5.3% vs 9.8%). Joint involvement represented the highest percentage in both sexes (84.2% vs. 75%) followed by skin involvement (68.4% vs. 71.7%) with photosensitivity (52.6% vs. 39.7%), malar rash (52.6% vs 54.9%), hematologic involvement (63.2% vs 72.8%), lupus nephropathy (15.8% vs 26.6%), pulmonary involvement (15.8% vs 35.4%). Pericarditis, ocular involvement and gastrointestinal involvement were each noted in a single case 5.3% vs 6.5%, 2.7%, 2.2% respectively in females.

In our series, autoimmune hemolytic anemia (AIHA) was more frequent in men compared to female (15.8% vs 8.7%). As well, leukopenia (31.6% vs. 20.7%) and thrombocytopenia (36.8% vs 21.7%). In contrast lymphopenia was less common in men (26.3% vs 32.6%).

Regarding the serological profile, the comparison of the positivity of the anti-native DNA antibodies in 19 male patients was high compared to female patients (n=102) (68.4% vs 55.4%). The prevalence of anti-Sm ($p = 0.053$), anti-Ribosome ($p = 0.028$) antibodies was significantly increased in men patients, while anti-SSA ($p = 0.003$), anti-SSB ($p = 0.011$) and anti-Histone ($p = 0.051$) were significantly increased in females patients.

The treatment included hydroxychloroquine in 18 cases (94.7%), corticosteroid therapy in 13 cases (68.4%) at a rate of 1 mg / kg / d for an average duration of 18 months with recourse to boluses of Solumédrol (1g / j × 3j) in 6 cases, associated with cyclophosphamide in 08 cases (42.1%). Non-steroidal anti-inflammatory drugs (NSAIDs) received in 02
cases and only one case received biotherapy based on Rituximab and IV immunoglobulins.

The course was marked by relapses in 10 cases (52.6%) of which 02 cases had corticosteroid-induced diabetes, 03 patients osteoporosis and 1 case progressed to end-stage renal disease. Complete remission was observed in 02 patients with a follow-up of 12, 24, 126 months. Regarding deaths during hospitalization, no case has been recorded. The survival at 1 and 5 years was respectively 100% and 80%.

In the female group (n = 184), the overall mortality was 4.89% (n = 9) during hospitalization. It was linked to cardiovascular involvement in 03 cases, end stage renal disease (04 cases) and two cases by ischemic stroke.

Table 1: Comparison of clinical manifestations in 203 men and women with SLE:

|                          | Male (n= 19) % | Female (n= 184) % | P value |
|--------------------------|---------------|-------------------|---------|
| Mean age                 | 33 ± 9.49     | 29.11 ± 11.36     | 0.044   |
| General signs            |               |                   |         |
| Fever                    | (11) 57.9     | (72) 39.1         | NS      |
| Asthenia                 | (03) 15.8     | (35) 19           | NS      |
| Weight loss              | (01) 5.3      | (18) 9.8          | NS      |
| Anorexia                 | (01) 5.3      | (18) 9.8          | NS      |
| Articular manifestation  | (16) 84.2     | (138) 75          | NS      |
| Dermatological disorders | (13) 68.4     | (132) 71.7        | NS      |
| Malar rash               | (10) 52.6     | (101) 54.9        | NS      |
| Photosensitivity         | (10) 52.6     | (73) 39.7         | NS      |
| Mucosal ulcer            | (10) 52.6     | (24) 13           | 0.000011|
| Alopecia                 | 0             | (41) 22.3         | 0.021   |
| Haematological disorder  | (12) 63.2     | (134) 72.8        | NS      |
| Raynaud’s syndrome       | (05) 26.3     | (47) 25.5         | NS      |
| Renal involvement        | (03) 15.8     | (49) 26.6         | NS      |
| Pericarditis             | (01) 5.3      | (12) 6.5          | NS      |
| Lung damage              | (03) 15.8     | (65) 35.3         | NS      |
| Neuropsychiatric         | (05) 26.3     | (12) 6.5          | 0.011   |

NS: non significatif

Table 2: Comparison of biological and serological abnormalities in 203 lupus males and females.

|                          | Male (n= 19) % | Female (n= 184) % | P value |
|--------------------------|---------------|-------------------|---------|
| Antinuclear antibody     | (19) 100      | (146/155) 79.3    | NS      |
| Anti-dsDNA               | (13) 68.4     | (102/155) 55.4    | NS      |
| Anti-Sm                  | (09) 47.4     | (48/155) 26.1     | 0.053   |
| Anti-RNP                 | (06) 31.6     | (32/155) 17.4     | NS      |
| Anti-SSA                 | (05) 26.3     | (62/155) 33.7     | 0.003   |
| Anti-SSB                 | 0             | (32/155) 17.4     | 0.011   |
| Anti Histone             | 0             | (16/155) 8.7      | 0.051   |
| Anti Ribosome            | (02) 10.5     | (4/155) 2.2       | 0.028   |
| APL                      | 0             | (25/155) 13.6     | 0.022   |
| Leucopenia               | (06) 31.6     | (38) 20.7         | NS      |
| Lymphopenia              | (05) 26.3     | (60) 32.6         | NS      |
| Thrombopenia             | (07) 36.8     | (40) 21.7         | NS      |
| AIHA                     | (03) 15.8     | (16) 8.7          | NS      |
| Hypocomplementemia       | (09) 47.4     | (59/78) 32.1      | 0.0004  |

Anti-dsDNA: anti-double-stranded DNA; AIHA: autoimmune hemolytic anemia; APL: anti-phospholipid; NS: non significatif
Table 3: Frequency of the main clinical and biological manifestations in our series and in the literature.

| ACR 1982 Criteria | Our study M% F% | Tunisia [14] M% F% | Europe (Cervera) [12] M% F% | North America (Kaufman) [11] M% F% | Latin America (Costallat) [29] M% F% | Asia (Kob) [30] M% F% | Asia (Pande) [31] M% F% |
|-------------------|-----------------|---------------------|-----------------------------|----------------------------------|----------------------------------|----------------------|----------------------|
| Number of patients | 19 | 184 | 24 | 271 | 92 | 908 | 52 | NA | 18 | 254 | 61 | 86 | 39 | 243 |
| Mean age attainment | 33 | 29.11 | 31.75 | 30.58 | NA | NA | 34 | NA | 21.36 | 26.53 | 28.2 | NA | 26 | NA |

ACR 1982 Criteria

- Malar rash %: 52.6 and 54.9
- Photosensitivity %: 52.6 and 39.7
- Mucosal ulcer %: 52.6 and 13
- Alopezia %: 0 and 22.3
- Raynaud’s syndrome %: 26.3 and 25.5
- Articular manifestation %: 84.2 and 75
- Renal involvement %: 15.8 and 26.6
- Pericarditis %: 5.3 and 9.2
- Neuropsychiatric %: 26.3 and 10.9
- Leucopenia %: 31.6 and 20.7
- Thrombopenia %: 36.8 and 21.7
- AIHA %: 15.8 and 8.7
- Anti-nDNA %: 68.4 and 55.4
- Anti-Sm %: 47.4 and 26.1
- Anti-RNP %: 31.6 and 17.4
- Anti-SSA %: 26.3 and 33.7
- Anti-SSB %: 0 and 17.4

Complementary Consumption %: 47.4 and 32.1

Table 4: Comparison of survival rate during SLE in humans.

| Author (reference) | case numbers | Number of deaths | 1 year | 5 years | 10 years | 15 years |
|--------------------|--------------|------------------|--------|---------|----------|---------|
| Kaufman [11]       | 52           | 15               | 98     | 91      | 71       | 59      |
| Koh [30]           | 61           | 04               | -      | -       | -        | -       |
| Pande [31]         | 39           | 02               | -      | -       | -        | -       |
| Wallace [32]       | 63           | -                | -      | 77      | 75       | 58      |
| Chang [33]         | 72           | -                | 84     | 76      | 75       | -       |
| Othmani [14]       | 24           | -                | 100    | 93      | -        | -       |
| Our study          | 19           | 0                | 100    | 100     | 100      | -       |

*: P significance level; M: male; F: female; NA: Data not available
**DISCUSSION:**

Our study is the first investigation of SLE in Algeria, it confirms the clinical and biological polymorphism of the disease in Algerian men and its similarity with other series in different regions of the world.

Lupus disease predominantly affects young women and rarely affects males. The female / male sex ratio was 9/1; 5/9; 10; 11; 11.5 and 9.6 in our series. The characteristic malar rash of Lupus was more frequent in males. Indeed, the positivity of native anti-DNA antibodies noted in 68.4% of cases is lower than that observed in Tunisia, Europe and North America. But significantly higher than in the continent of India and Latin America. The leukopenia observed in 31.6% of our patients is higher than those in India and Latin America and lower than those in Tunisia and North America. Thrombocytopenia noted in 36.8% of cases is higher than the percentages noted in Tunisia, North and Latin America and India.

The haematological manifestations observed in our series are comparable to the literature. It was noted in 63.2% of cases. The hemolytic anaemia characteristic of SLE was noted in 15.3% of cases, close to those of Tunisia, Europe and North America, and higher than those of Singapore and India. The leucopenia observed in 31.6% of our patients is higher than those in India and Latin America and lower than those in Tunisia and North America. The positivity of native anti-DNA antibodies noted in 68.4% of cases is lower than that observed in Tunisia, Europe and North America. But significantly higher than in the continent of India and Latin America, Singaporean and Latin American population. Another serological marker of anti-Sm antibody was found positive in 47.4% of cases in our population. This result is similar to that noted in Tunisia, but higher than that noted in the European, Singaporean, and North American populations.

From an evolutionary standpoint, we have noted drug complications related to the treatments administered by our patients. Two cases treated with corticosteroids (Prednisone) developed corticosteroid-induced diabetes, three cases of osteoporosis and only 1 case progressed to end-stage renal disease.

The overall survival of male lupus is reported in Table 4. In our series during the selected study period (2006-2019), survival is equal to 100%, identical to that in Tunisia in the first year. In addition, in the female sex, the overall mortality was 4.89% (n = 09). Survival at 1/5 and 10 years was 100%/94%/76% respectively.

The statistical comparison of our series with studies in the literature is provided for information only. Indeed, the clinical signs are not examined under the same conditions in all the studies, the prevalence of clinical and biological manifestations varies according to the time of diagnosis, the clinical services from which the patients come are not homogeneous, and even the immunological tests are not made under the same conditions and techniques.

**CONCLUSION:**

Algerian men with SLE have a less severe form compared to other studies in the literature, which is manifested by a lower frequency of organic attacks. Further prospective studies are needed with larger numbers to better understand this disease in humans and to assess the effectiveness of treatments.

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