Original Contribution/Clinical Investigation

Late onset Systemic Lupus Erythematosus: Tunisian cohort

Hammami Sonia
Yaich Amine
Klii Rym
Kechida Malek
Arfa Sondes
Ben Nasr Maha

Department of Internal Medicine,
Fattouma Bourguiba University Hospital,
University of Monastir, Tunisia

Corresponding author:
Prof. Sonia Hammami
Telephone number: 0021698913188
Email: sonia.hammami@fmm.rnu.tn

ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is usually described as a disease that most often strikes reproductive-age women. However, SLE can be observed in children and in the elderly. Late onset of systemic lupus erythematous(SLE) seems to differ from young onset disease. We discuss the clinical course, immunological features, treatment and prognosis of SLE in the older population.

Methods: We conducted the current study to analyze characteristics and outcome of patients with late onset SLE in a Tunisian tertiary referral center, and to compare them with patients younger than 50 years at SLE diagnosis. This cross-sectional study consisted of 83 SLE patients (75 female and 8 male), who attended the Department of Internal Medicine in Monastir between 2006 and 2015.

Results: 12 patients were identified as having late-onset SLE, diagnosed at or over the age of 50 years. These patients were compared with a group of 71 young patients at SLE diagnosis. We compared clinical features, laboratory data, management and course.

Elderly patients less often presented with malar rash, photosensitivity, and nephropathy. Regarding laboratory features, older patients have a higher frequency of rheumatoid factor compared with young SLE patients. Whereas, leukopenia was less frequent in the older population

Deaths occurred more frequently in late-onset SLE ($p = 0.02$); the main causes of death were infectious complications.

Conclusion: Late-onset SLE is characterized by a lower severity of disease. The poorer prognosis of late-onset SLE contrasting with the lower severity of the disease seems to result mainly from the consequences of aging.

Key words: Late onset, early onset, systemic lupus erythematosus; elderly

Introduction

Systemic lupus Erythematosus (SLE) is an autoimmune disease with wide clinical features. The diagnosis of SLE is based on American College of Rheumatology (ACR) and SLICC criteria. SLE affects usually young adults. Few reports studied SLE in the elderly [1,2,3,4].

We enrolled a retrospective study to establish the epidemiological, clinical and laboratory profile, therapeutic and prognostic aspects and course disease of late onset SLE. The aim of our study is to compare the different presentations of SLE in old and young population.

Patients and Method

We conducted a cross-sectional study that consisted of 83 SLE patients (75 female and 8 male), who attended the Department of Internal Medicine in Monastir University Hospital between 2006 and 2015. All patients met at least 4 criteria of the American College of Rheumatology (ACR/SLICC) revised criteria of SLE [5]. Patients with drug-induced SLE or pure cutaneous lupus were excluded. Patients with diagnosis of SLE at the age of 50 or later were classified as the "late onset" lupus, all patients aged younger than 50 years at SLE diagnosis, constituted the ''early-onset'' SLE group. All patients underwent a physical examination. In addition to routine laboratory investigations including tests were conducted for rheumatoid factor, antinuclear antibody (indirect immunofluorescence method with HEp-2 cells as substrate), complements 3 and 4, anticardiolipin antibodies, and lupus anticoagulant. Other several examinations such as an echogram and computerized tomography were performed, if needed. The following items were recorded: age at the onset of the disease, sex, date of diagnosis, clinical and laboratory manifestations and the status at the last visit. Organ involvement not related to SLE was excluded. The SLE disease activity index (SLEDAI) was used to measure the severity of disease at the time of diagnosis [6].

Statistical analysis: The data were analyzed statistically using SPSS software for Windows (version 18) to compare the epidemiological, clinical and laboratory parameters in different groups. A Fisher exact test was performed for qualitative variables, and a Student t-test for comparison of quantitative variables. Statistical significance was defined as $p \leq 0.05$.

Results

From the total of 83 (75 female and 8 male) patients included in this study, 12 patients were identified as having late-onset SLE; mean age at SLE diagnosis was 58.4 ± 5.8 years (range, 51-72 yr.). The early onset control group n= 71 (mean age 31.8 ± 10 years, range 16-49). There was no significant difference in gender distribution among the groups (Table 1).

The duration between disease onset and diagnosis was 26 months (range, 11-48) for the old patients, compared with 10 months (range, 3-24) in the younger SLE group. This difference was statistically significant (p=0.01). Mean number of revised ACR criteria was smaller for the older population compared to the younger one (4.9 ± 0.6 vs 6.8± 0.9; p = 0.04),

Clinical manifestations at diagnosis in both groups are summarized in Table 2 (next page).

In the Late onset group lupus showed a significantly less frequency of malar rash (33.3% vs 70.4 %; p=0.01), photosensitivity (41.6% vs 73.2 %; p=0.02) and lupus nephritis (8.3 % vs 36.6 %; p= 0.04) compared with the early-onset group.

Table 1 : Demographic characteristics of SLE in late and early onset patients

	Late onset (n=12)	Early onset (n = 71)	p value
Mean age (years)	58.4 ± 5.8	31.8 ± 10	--
Sex-ratio F/M	11/1	64/7	0,86
Delay diagnosis*	26±9.4	10±6.4	0,01
SLEDAI	8.1	9.4	0.5
ACR Criteria	4.9 ± 0.6	6.8± 0.9	0.04
Mean years of follow up	6.8 ± 5.2	9.5 ± 5.8	0,02

*delay between SLE onset and diagnosis, F/M: female/male

Table 2 : Clinical manifestations at the diagnosis of SLE in late and early onset patients

	Late onset, n=12 No. of patients (%)	Early onset, n= 71 No. of patients (%)	p value
Fever	4 (33,3)	19 (26.7)	NS
Weight loss	3(25)	20(28)	NS
Malar rash	4 (33,3)	50 (70,4)	0,01
Photosensitivity	5 (41,6)	52 (73,2)	0.02
Mucosal ulcer	1 (8,3)	11 (15,4)	NS
Discoid lupus	2 (16,6)	8 (11,2)	NS
Alopecia/hair loss	2 (16,6)	9 (12,6)	NS
Arthritis	8 (66)	48 (67,6)	NS
Lupus nephritis*	1 (8.3)	26 (36.6)	0,04
Pericarditis	5 (41,6)	16 (22,5)	NS
Pleuritis	3 (25)	16 (22,5)	NS
Lung involvement	5 (41,6)	19 (26,7)	NS
Neurological involvement	3 (25)	16 (22,5)	NS
Ocular involvement	3 (25)	9 (12,6)	NS
Thrombosis	4 (33,3)	11 (15,4)	NS
Pulmonary embolism	1 (8,3)	4 (5,6)	NS

*Proliferative glomerulonephritis (WHO class II, III or IV)

Laboratory Findings

Regarding laboratory findings at the time of onset of SLE (Table 3), the late-onset group was characterized by a lower frequency of leukopenia (25% vs 55 %; p=0.05). The other hematological disorders (lymphopenia, hemolysis anemia and thrombocytemia) were slightly less frequent compared to the early-onset group, but differences were not significant. Whereas rheumatoid factor positivity occurred more frequently in the elderly. No significant differences were found for anti-dsDNA, anti-Sm, and antiphospholipid antibodies

Table 4 summarizes the main concomitant auto-immune diseases associated to SLE. The late onset of lupus was associated with increased incidence of rheumatoid arthritis (33.3 % vs 7%; p=0.007). APS and Sjogren syndrome were slightly more frequent compared to the early-onset group.

Therapy and Course

High-dose corticosteroids >1mg/kg/day (42.2 % vs. 18 %; p = 0.05) and hydroxychloroquine (92.9 % vs 75 %; p = 0.007) were less frequently used in the late-onset group. The late onset of lupus was associated with increased incidence of hypertension, diabetes, osteoporosis and infections. At the time of analysis, 3 patients had died in the late onset group of which 3 were infections, and only 4 patients in the early onset group (p=0.02). None of our late-onset SLE patients died of SLE flare.

Discussion

SLE has been considered to be a disease of young women. Late onset SLE is less frequent. From the total of 83 SLE patients in this study, twelve late-onset SLE patients, that is, diagnosed at or over the age of 50 years, represented 14.4% of all patients with SLE followed in our department. Different incidences have been reported (3.6-20 %). This may be related to the lack of strict definition of late-onset SLE. The cutoff age used most frequently is 50 years at disease or diagnosis [1,2, 7,8]. The female-to male ratio declines but not significantly with age in our study. In most of the literature data, the female to male ratio was significantly lower in the late onset group [7]. This probably reflects the relationship between SLE and estrogen status [8-9]. Oestrogens have multiple immunomodulatory effects. There was a significant delay in the diagnosis of SLE in older ages. This longer interval may be related to the atypical presentation

Table 3: Laboratory findings of SLE in late and early onset patients

	Late onset, n=12 No. of patients (%)	Early onset, n= 71 No. of patients (%)	p value
Inflammatory syndrome	8 (66,6)	47 (66,1)	NS
Hemolysis Anemia	0 (0)	3 (4,2)	NS
Leukopenia<4000/mm3	3 (25)	39 (55)	0,05
Lymphopenia	8 (66,6)	58 (81,6)	NS
Thrombocytopenia*	1 (8,3)	9 (14,5)	NS
Hypocomplementemia	3 (25)	17 (23,9)	NS
Antinuclear antibodies	12 (100)	65 (91,5)	NS
Anti-DNA antibodies	9 (75)	57 (80,2)	NS
Rheumatoid factor	4 (33,3)	12 (16.9)	NS
Anti-Sm antibodies	2 (16,6)	26 (48,1)	NS
Anti-SSA antibodies	5 (41,6)	35 (63,6)	NS
Anti-SSB antibodies	4 (33,3)	23 (41,8)	NS
Anti-RNP antibodies	2 (16,6)	20 (37,7)	NS
Anticardiolipin antibodies IgG	4 (33,3)	24 (35,2)	NS
Anti- β2GPI	4 (33,3)	13 (18)	NS

Table 4 : Autoimmune diseases associated with SLE in late and early onset patients

	Late onset, n=12 No. of patients (%)	Early onset, n= 71 No. of patients (%)	p value
Rheumatoid arthritis	4 (33,3)	5 (7)	0,007
APS *	3 (25)	13 (18,3)	NS
Sjögren's syndrome	4 (33,3)	18 (25,3)	NS
Thyroiditis	2 (16,6)	11 (15.4)	NS
Scleroderma	0 (0)	2 (2,8)	NS

Table 5 : Complications that occurred during follow up in late and early onset patients

	Late onset, n=12 No. of patients (%)	Early onset, n= 71 No. of patients (%)	p value
Osteoporosis	7 (58,3)	6 (8,4)	0,0001
Hypertension	6 (50)	7 (9.8)	0,001
Diabetes	5 (41.6)	11 (15,4)	0,04
Infection	8 (66)	18 (25.3)	0,002
Death	3 (25)	4 (5,6)	0,02

of SLE in the older population. The disease seems to be mild with lower SLE criteria compared to the younger group. Similar results have been reported by many other studies [8, 10].

Age at disease onset of SLE influenced the clinical manifestations and serological laboratory findings. The result of our study shows that older population less often presented with malar rash, photosensitivity, and nephropathy. Most of the literature data segregating early and late onset group, show lower rates of nephritis, malar rash, photosensitivity, arthritis and less visceral involvement with more benign course in the older group, whereas, pulmonary involvement and serositis are more frequently observed [8, 10, 11, 12] . The results of our study support the concept that late onset lupus is less active in the older population [10- 16].

Regarding laboratory results, Leukopenia was significantly more frequent in the early onset group, whereas rheumatoid factor positivity was more frequent (33.3 % vs. 16.9 %) in old compared with young SLE patients, but the difference was not statistically significant, although no difference was found for other autoantibody frequencies (anti DNA, anti-Sm, anti-RNP, SSA and anti-SSB antibodies). Das Chagas Medeiros MM et al reported leuko/lymphopenia most frequently in late onset lupus but Appenzeller et al. reported hemolytic anemia and thrombocytopenia most frequently in late-onset SLE. Lalani et al. found no difference between the groups when comparing lymphopenia and thrombocytopenia [15, 17-18].

It should be noted that, it is difficult to be conclusive with regard to autoantibody findings, since they were not measured in the same laboratory. For the rheumatoid factor, most publications agree in indicating its higher frequency in patients with late-onset SLE [7, 19, 20], However, it should be noted that this is probably related to the prevalence of increased rheumatoid factor positivity in the elderly population. The literature is rather inconsistent with regard to the predominant serological profile in early and late onset SLE. Our study found no differences in the autoantibody profile in the two groups. Boddaert J et al reported a higher frequency of anti-RNP, anti-Sm and rheumatoid factor with a lower frequency of hypocomplementemia in late-onset SLE [7]. Appenzeller et al. reported a lower frequency of anti-Ro in late-onset SLE, while Alonso MD et al reported a lower frequency of positive anti-DNA [17,21]. Lower positive rates of autoantibodies and less frequent hypocomplementaemia may indicate milder disease activity in older population [3, 21]. Some series reported a higher prevalence of positive anti-Ro/SSA and/or anti-La/SSB antibodies [22-25]. In the present investigation, there were no differences in the frequency of Sjogren's syndrome among the group of late-onset SLE and the group of early-onset SLE patients, but rheumatoid arthritis was more associated to late onset SLE. Another cohort reported a higher frequency of Sjogren's syndrome in their populations with late-onset SLE [19, 27]; Boddaert J et al in their pooled data analysis, reported that Sjögren's syndrome was more frequently present in the late-onset than in the early-onset SLE, although no difference was found for anti-SSA and anti-SSB antibodies [7]. The lack of a parallel increase in Sjogren's autoantibodies in these patients may reflect the aging process, in fact the sicca symptoms may be related to other more frequent causes of mucosal dryness in the elderly population, such as senile salivary gland atrophy, polypharmacy and chronic debilitating diseases [27, 28].

Hypertension, diabetes and osteoporosis were significantly more increased in the late onset group than in the early onset group in our cohort. The greater frequency of age related comorbidities in older population is due to aging and longer exposure to classical risk factors and use of corticosteroids [7,29]. In our cohort, the mortality rate was greater in the late onset group; infection caused death in 3 of 4 patients. The higher mortality in older patients contrasting with the lower severity of the disease, may be related to the fact that lupus at that age may be complicated by co-morbidities and increased risk of toxicities from immunosuppressive drugs usually used.

In our study glucocorticoids, hydroxychloroquine use was less frequent in the late-onset group compared to the early-onset group.

Our study has some limitations. First the validity is limited by the retrospective design; the collection of the data may have underestimated the frequency of some clinical manifestations. Second, the size of our sample is quite small; it is representative only for the population of the center of Tunisia. We also acknowledge that there may have been changes to medications or co-morbidities outside our hospital.

In summary, this study in the Tunisian SLE population showed that age affects the expression of SLE. Late onset SLE has a milder disease compared with early onset group, characterized by less renal, photosensitivity and malar rash. However, the mortality rate of older population is higher. Co-morbidities such as hypertension, diabetes and osteoporosis were significantly more frequent in late-onset SLE.

References

1-Louzir B, Othmani S, Ben Abdelhafidh N et al. Le lupus érythémateux systémique en Tunisie.
Étude multicentrique nationale. Rev Med Interne 2003; 24: 768-774.

2-Maddison P.J. Systemic lupus erythematosus in the elderly. J Rheumatol 1987; 14: 182-187.

3- Chen TL, Wong CH, Lee Ch et al. Systemic lupus erythematosus in the elderly. Gerontology
2009 ; 3:108-113.

4-Dieval C, Ribevio O, Grenouillet MD et al. Lupus du sujet âgé : étude descriptive clinic biologique à partir de 44 cas. Rev Med Interne 2008 ; 29 : 294-336 .

5- Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677-86.

6-Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum. 1996;39(3):363-9.

7- Boddaert J, Huong DL, Amoura Z, Wechsler B, Godeau P, Piette JC. Late-onset systemic lupus erythematosus: a personal series of 47 patients and pooled analysis of 714 cases in the literature. Medicine. 2004;83(6):348-59.
8-Sassi RH, Hendler JV, Piccoli GF, Gasparin AA, da Silva Chakr RM1, Brenol JC et al. Age of onset influences on clinical and laboratory profile of patients with systemic lupus erythematosus. Clin Rheumatol. 2017 ;36(1):89-95.
9- Cartella S, Cavazzana I, Ceribelli A, Inverardi F, Tincani A, Franceschini F. Evaluation of mortality, disease activity, treatment, clinical and immunological features of adult and late onset systemic Lupus erythematosus. Autoimmunity. 2013;46(6):363-8.
10-Choi JH, Park DJ, Kang JH, Yim YR, Lee KE, Lee JW et al. Comparison of clinical and serological differences among juvenile-, adult-, and late-onset systemic lupus erythematosus in Korean patients. Lupus 2015, 24 (12), 1342-49.
11-Medlin JL1, Hansen KE2, Fitz SR3, Bartels CM. A systematic review and meta-analysis of cutaneous manifestations in late- versus early-onset systemic lupus erythematosus. Semin Arthritis Rheum. 2016 Jun;45(6):691-7.
12-Zulfiqar AA1, Courtel T1, Novella JL1, Pennaforte JL1. Late-onset lupus in the elderly after 65 years: retrospective study of 18 cases. Geriatr Psychol Neuropsychiatr Vieil. 2015 ;13(2):157-68
13- Stefanidou S, Gerodimos C, Benos A, Galanopoulou V, Chatziyannis I, Kanakoudi F, et al
Clinical expression and course in patients with late onset systemic lupus erythematosus. Hippokratia. 2013 ;17(2):153-6.
14- Sousa S, Gonçalves MJ, Inês LS, Eugénio G, Jesus D, Fernandes S et al. Clinical features and long-term outcomes of systemic lupus erythematosus: comparative data of childhood, adult and late-onset disease in a national register. Rheumatol Int. 2016 ;36(7):955-60.
15- das Chagas Medeiros MM, Bezerra MC, Braga FN, da Justa Feijão MR, Gois AC, Rebouças VC, et al . Clinical and immunological aspects and outcome of a Brazilian cohort of 414 patients with systemic lupus erythematosus (SLE): comparison between childhood-onset, adult-onset, and late-onset SLE. Lupus. 2016 ;25:355-63.
16-Catoggio LJ, Soriano ER, Imamura PM, Wojdyla D, Jacobelli S, Massardo L, et al. Late-onset systemic lupus erythematosus in Latin Americans: a distinct subgroup? Lupus 2015;24(8):788-95
17- Appenzeller S Pereira DA, Costallat LT. Greater accrual damage in late-onset systemic lupus erythematosus: A long-term follow-up study. Lupus 2008; 17: 1023-28
18- Lalani S, Pope J, de Leon F, Peschken C;. Members of CaNIOS/1000 Faces of Lupus. Clinical features and prognosis of late-onset systemic lupus erythematosus: Results from the 1000 faces of lupus study. J Rheumatol 2010; 37: 38-44
19- Maddison P, Farewell V, Isenberg D, The rate and pattern of organ damage in late onset systemic lupus erythematosus. J Rheumatol 2002; 29: 913-17
20- Peñaranda-Parada E, Quintana G, Yunis JJ, Mantilla R, Rojas W, Panqueva U et al
Clinical, serologic, and immunogenetic characterization (HLA-DRB1) of late-onset lupus erythematosus in a Colombian population.Lupus. 2015 ;24:1293-9
21-Alonso MD, Martinez-Vazquez F, de Teran TD, Miranda-Filloy JA, Dierssen T, Blanco R et al. Late-onset systemic lupus erythematosus in Northwestern Spain: differences with early-onset systemic lupus erythematosus and literature review. Lupus. 2012 Sep;21(10):1135-4821-
22- Mak SK, Lam EKM, Wong AKM. Clinical profile of patients with late-onset SLE: not a benign subgroup. Lupus 1998; 7: 23-28.
23- Shaikh SK, Wang F. Late-onset systemic lupus erythematosus: clinical and immunological characteristics. Med J Malaysia. 1995;50:25-31.
24- Ward MM, Studenski S. Age associated clinical manifestation of SLE: a multivariate
regression analysis. J Rheumatol 1990;17:476-81.
25- Lazaro D. Elderly-onset systemic lupus erythematosus: prevalence, clinical course and
treatment. Drugs Aging: 2007; 24(9):701-15.
26-Strickland RW, Tesar JT, Berne BH, Hobbs BR, Lewis DM, Welton RC. The frequency of
sicca syndrome in an elderly female population. J Rheumatol 1987; 14: 766-71.
27- Padovan M, Govoni M, Castellino G, Rizzo N, Fotinidi M, Trotta F. Late onset systemic
lupus erythematosus: No substantial differences using different cut-off ages. Rheumatol
Int 2007; 27: 735-41
28- Achour A, Mankaï A, Thabet Y, Sakly W, Braham F, Kechrid C, et al. Systemic lupus erythematosus in the elderly. Rheumatol Int. 2012 ;32:1225-9.
29- Merola JF, Bermas B, Lu B, Karlson EW, Massarotti E, Schur PH, Costenbader KH.
Clinical manifestations and survival among adults with (SLE) according to age at diagnosis.
Lupus. 2014 ;23:778-84
30- Abu-Shakra M, Urowitz MB, Gladman DD, Gough J. Mortality studies in systemic lupus erythematosus. Results from a single center. I. Causes of death. J Rheumatol. 1995;22:1259-64.