ORIGINAL ARTICLE

Late-Onset Systemic Lupus Erythematosus: Clinical and Immunological Characteristics

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Summary

Between January 1976 and December 1992, 17 patients on follow-up at Systemic Erythematosus (SLE) Clinic in the University Hospital, Kuala Lumpur had onset of the disease after the age of 50 years. This constituted about 4% of our total SLE patients. They formed a distinct subgroup of the lupus population with an insidious onset and have a benign course compared to the younger SLE patients. Arthritis and skin rashes were the commonest initial manifestations. Renal and central nervous system manifestations were uncommon but pulmonary involvement was frequent compared to young SLE patients. The prevalence of positive autoantibodies and hypocomplementaemia were lower. Disease activity showed no correlation with erythrocyte sendimentation rate, autoantibodies or complement levels. Overall prognosis in these late-onset patients was favourable with a good response to steroids and less frequent relapses.

Key Words: Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) was first described by Kaposi in 1872[1]. The modern era of SLE however began in 1948 with the discovery of the lupus erythematosus cells (LE cells) by Hargraves *et al*[2]. This led to the identification of more cases of SLE and subsequent recognition of wider variability of the disease manifestations. As the course of the disease is characterised by marked variability, a recent trend has been to identify subsets of patients with SLE[3]. One subset which has not received much attention comprises of those patients whose disease are of late onset i.e. after the fifth decade.

This study describes the clinical and laboratory characteristics and treatment outcome of local patients with late-onset SLE.

Subjects and Methods

This is a retrospective review of all SLE patients followed up at the University Hospital, Kuala Lumpur between 1st January 1976 till 31st December 1992. During this period 17 patients were diagnosed to have SLE with onset after the age of 50 years i.e. late-onset SLE. All the patients met the 1982 revised American Rheumatism Association criteria for SLE[4].

Detailed histories and thorough physical examinations were performed at the first and subsequent follow-up. Laboratory tests included full blood counts, erythrocyte sendimentation rate, urinalysis, blood urea nitrogen, serum creatinine and 24-hour urine protein. Antinuclear antibodies (ANA) titre and staining pattern, anti-deoxyribonucleic acid (anti-dsDNA) and serum complements (C3 and C4) were done in all

the patients. Antinuclear antibodies were determined by indirect immunofluorescence technique. Antibodies to dsDNA were determined by Farr's ammonium sulphate precipitation technique. Complement components (C3 and C4) were estimated by radial immunodiffusion method. Ribonucleoprotein (RNP), Rheumatoid Factor, Venereal Disease Research Laboratory test (VDRL), anti-cardiolipin, lupus anticoagulant, anti-Ro (SSA), anti-La (SSB), and anti-Sm (SSB) were done on selected patients. The anticardiolipin antibodies were measured by an enzyme-linked immunosorbent assay (ELISA) method. The lupus anticoagulant was detected by both kaolin activated partial thrombin time and using the Russell pit viper venom. Percutaneous renal biopsy were performed on five patients who had clinical evidence of renal involvement. Respiratory functions tests were done on two patients.

The patients' records were analysed with regards to clinical presentation, laboratory findings and outcome of treatment. Patients with drug-induced lupus, discoid lupus alone or "overlap syndrome" were excluded. The onset of SLE was defined by the date of diagnosis and by the date of probable onset i.e. the initial characteristic manifestations of the disease. Both onset and diagnosis had to occur after the patient's 50th birthday in order for the patient to be included in this study. Arthritis was defined as joint swelling, tenderness or pain on motion. Renal involvement was defined clinically by at least one of the following:- proteinuria of 0.5gm or more per 24 hours, microscopic haematuria with more than 10 red blood cells per high power field, red cell casts or a serum creatinine greater than 150 umol/l.

The control group consisted of 52 SLE patients with onset of disease between the age 20 and 50 years. They were selected from 500 SLE patients who were on follow-up at the University Hospital Kuala Lumpur during the same period. They were each given a number and the first 52 numbers drawn from a box containing the 500 numbers were selected for this study.

Statistical analysis

Chi-square test was used for analysing qualitative differences and Student's t test was used for comparison of quantitative data.

Results

Patient characteristics

There were a total of 17 SLE patients with onset of the disease after the age of 50 years. Of these, 16 were Chinese and one was Malay. All were female. In the control group which consisted of 52 young SLE patients, 49 were Chinese, two Malays and one Indian.

The mean age of onset for the late-onset SLE was 56.8 ± 3.3 years. The mean age of diagnosis was 59.1 ± 3.8 years. In the control group the mean age at onset of disease was 27 ± 4.3. The mean interval from onset to diagnosis in the late-onset group was 55 ± 4 weeks. In the control group the mean interval was 7.3 ± 5.1 weeks. 58% of the late-onset SLE were diagnosed within one year of presentation while all the young lupus patients were diagnosed within a year of presentation.

Clinical manifestations

Table I shows the initial presenting clinical manifestation for patients with disease onset before and after the age of 50. The late onset group had nephritis less often as the first symptoms ($p<0.05$). Follow-up analysis of the cumulative clinical symptoms revealed that the most significant difference between the two groups was a significantly lower prevalence of nephritis ($p<0.005$) amongst the late-onset group. In contrast this group has a significantly higher prevalence of pulmonary involvement ($p<0.001$).

The occurrence of other clinical features including rash, arthritis, central nervous system manifestations, mouth ulcers, myositis, Raynaud's phenomenon, haemolytic anemia, lymphadenopathy, thrombotic events did not differ significantly between the two groups (Table II).

Immunological abnormalities

Table III gives the serological findings in relation to age. High titres of anti-dsDNA occurred less frequently in the late onset group ($p<0.001$) despite similar proportions of clinically active cases in both groups. Similarly hypocomplementaemia (C3 and C4) was less

Table I
Presenting clinical manifestations in late-onset SLE and young

Presenting clinical manifestations	SLE patients		P
	late-onset group n=17 (%)	young lupus n=52 (%)	
Rash	8 (47)	17 (32.7)	NS
Arthritis	7 (41.2)	20 (38.5)	NS
Nephritis	0 (0)	11 (21.2)	<0.005
Central nervous system (stroke)	1 (5.9)	0 (0)	NS
Bleeding (thrombocytopenia)	1 (5.9)	3 (5.8)	NS
Immune hemolysis (AIHA)	0 (0)	3 (5.8)	NS

Table II
Cumulative clinical features in late-onset SLE compared with the young SLE patients

Clinical features	late-onset SLE n=17 (%)	young SLE n=52 (%)	P
Skin rash	12 (70.6)	40 (70.7)	NS
Arthritis	9 (52.9)	32 (61.5)	NS
Renal	5 (29.4)	34 (65.4)	<0.005
Pulmonary	7 (41.1)*	2 (3.8)	<0.001
Neuropsychiatry	2 (11.8)	12 (23.0)	NS
Mouth ulcers	5 (29.4)	17 (3.2)	NS
Alopecia	8 (47.0)	30 (57.7)	NS
Raynaud's phenomenon	0 (0.0)	2 (3.8)	NS
Lymphadenopathy	2 (11.8)	6 (11.5)	NS
Thrombotic events	1 (5.9)+	2 (3.8)#	NS
Cardiovascular	0 (0.0)	1 (1.9)	NS
Autoimmune hemolysis	1 (5.9)	4 (7.9)	NS
Myositis	0 (0.0)	1 (1.9)	NS
Hepatomegaly	1 (5.9)	3 (5.8)	NS

\+ *presented with digital gangrene.*
\# *one presented with recurrent pulmonary embolism and another with multiple thromboses involving liver, spleen and renal veins.*
* *one presented with pleural effusion and six others had pneumonitis.*

commonly seen in the late onset group ($p<0.001$). The incidence of antiphospholipid antibodies (anticardiolipin and lupus anticoagulant), anti-Ro, anti-La, anti-Sm and Ribonucleoprotein (RNP) did not differ significantly between the two groups.

Haematological abnormalities

Table III also shows the haematological findings in patients with disease onset before and after the age of 50. There is a significantly lower prevalence of an elevated ESR in the late-onset group compared to the young SLE group ($p<0.001$). However there is no significant difference in other haematological parameters including thrombocytoapenia, anaemia, leucopaenia, Coomb's test and VDRL.

Response to treatment

Table IV shows the outcome of treatment in the two patient subgroups. The late onset-lupus responded better to treatment and experienced fewer relapses compared to the younger patients.

Discussion

Systemic lupus erythematosus (SLE) is most prevalent amongst patient between 20 to 40 years of age. The disease is nine times more common in females than in males[5]. It is rare in the older age groups[6,7,8,9] and the diagnosis is not often thought of in the older patient. The division between young and old is arbitrary and differs from one study to another. The

Table III
Haematological and serological features of late-onset SLE compared with young SLE patients

Hematological and serological features	SLE patients		P
	late-onset n=17 (%)	young n=52 (%)	
Anemia	9 (52.9)	41 (78.8)	<0.05
Autoimmune hemolytic anemia	1 (5.9)	4 (7.6)	NS
Positive Coomb's test	1 (5.9)	8 (15.4)	NS
Leucopenia	11 (64.0)	28 (53.8)	NS
Thrombocytopenia	6 (35.0)	16 (30.8)	NS
Hypocomplementaemia	11 (64.0)	52 (100)	<0.001
Antinuclear antibodies	14 (82.0)	52 (100)	NS
Anti-dsDNA	10 (58.8)	52 (100)	<0.001
Anti-Ro (SSA)	1 (5.9)	7 (13.4)	NS
Anti-La (SSB)	1 (5.9)	0 (0)	NS
Anti-Sm	0 (0)	1 (1.9)	NS
RNP	2 (11.7)	0 (0)	NS
Anticardiolipin	6 (35.0)	7 (13.4)	NS
Lupus anticoagulant	0 (0)	1 (1.9)	NS
VDRL (false positive)	10 (58.8)	52 (100)	NS

Table IV
Outcome of treatment: late-onset SLE compared to young SLE patients

Response to treatment	SLE patients		P
	late-onset n=17 (%)	young n=52 (%)	
Remission with no relapse	14 (77.0)	21 (40.0)	<0.005
Remission with 1 or more relapses	3 (23.0)	31 (60.0)	<0.005

Table V
Clinical features of late-onset SLE of our patients as compared to other series

Clinical Features	This study (%)	late-onset SLE patients I[12] (%)	II[28] (%)	III[6] (%)	IV[2] (%)	V[7] (%)
Arthritis	52.9	94	98	62	88	95
Rash	70.6	65	84	86	79	81
Nephritis	41.1	55	84	86	79	81
Pulmonary	41.4	85	66	31	64	73
Neuropsychiatry	11.8	26	50	40	37	59
Alopecia	47.0	26	64	38	41	37
Hepatomegaly	5.9	23	–	–	–	25
Mouth ulcers	29.4	13	34	29	–	36
Adenopathy	11.8	10	30	40	19	21
Raynaud's phenomenon	0	10	32	45	23	21
Thrombotic events	5.9	–	–	–	–	–
Cardiovascular	0	–	–	–	–	–
Myositis	0	–	–	–	–	–
Hemolytic anemia	5.9	–	–	–	–	–

frequency of SLE among older age groups ranges from 7-18%[6,7,8,9]. Recent limited studies describing lupus in the older age group have been conflicting concerning pattern of presentation, organ involved and prognosis. This is not surprising since the disease is characterised by a wide spectrum of clinical manifestations and the number of patients reported in each series is relatively small. Nevertheless the consensus is age appears to influence the clinical and serological expressions of the disease.

In our study late-onset SLE constituted only 4% of the total lupus patients. This is lower compared to the 7-18% from cases compiled from other series[6,7,8,9].

Like their younger counterparts, late-onset lupus patients showed a marked female preponderance. All our patients were female. This is in contradiction to that reported by most other authors who have observed the loss of female preponderances in this late-onset lupus patients[8,10,11]. In fact Joseph *et al*[12] in 1964 described cases of late onset SLE with male preponderance. However reports of Kellum *et al*[6] and Stuart *et al*[13] in which female accounted for 79% and 81% respectively of patients over the age of 50 show that lupus in the older age group has the same female preponderance as lupus in the young.

Onset of SLE among the late onset group tend to be more insidious than the younger patients[5,14-21]. The interval between onset of symptoms to diagnosis was on the average 55 weeks compared to 7 weeks amongst the younger patients. Urowitz *et al*[22] evaluated the influence of age on the clinical pattern of SLE and found that SLE in the older age seemed to be a milder disorder with a longer duration of symptoms and a lower corticosteroid requirement. McCombs and Patterson[23] noted an inverse correlation between the severity of SLE and the age of patients at diagnosis. Other authors[12,13,15] have also found late-onset SLE to be insidious in onset and to be a more benign disease as measured by corticosteroid dosage requirements and outcome. They therefore recommended a conservative approach to therapy for older patients with lupus. The estimated five-year survival of 92.3% and nine-year survival of 83.1% support the contention that SLE in the older age group has a more favourable outcome[13].

The clinical expressions of SLE in older patients differs from those in young SLE subset. Some series have reported that the presenting manifestations resemble those in patients with drug-induced SLE, polymyalgia rheumatica or Sjogren's syndrome[14,16,19,20]. In our study rash and arthritis were the commonest initial presentations but these were also observed in the young lupus group. The most interesting finding in our study was unlike in our young lupus patients, nephritis was significantly a less common initial presenting manifestation. This finding concurs with those reported in several other series[5,14,19,24] but is not a universal feature[3,7,8,19].

Pulmonary involvement was common in our late-onset SLE patients. In 1972, Urowitz *et al*[7] highlighted that parenchymal pulmonary involvement was more frequent in the older patient. Foad *et al*[15] reported that pleuritis and/or pericarditis were the most common presenting manifestation in their series followed by arthritis, rash hematological abnormalities and constitutional symptoms[15]. The relatively common pulmonary involvement in the older patients was further substantiated by Stuart's series in which one third of his patients has pulmonary involvement[13].

Several authors have reported a lower incidence of central nervous system among older SLE patients[13,14,17]. This however was not seen in our study. Table V compares the clinical features of our patients with that of five other series.

Age also influences the serological manifestations of SLE. Lower anti-dsDNA titres were found in our study patients. Similar results have been reported by Cotaggio *et al*[18], Wilson *et al*[15] and Font *et al*[24]. It has been suggested that anti-Ro and anti-La antibodies are more prevalent[18] in the older lupus patients and might be a useful diagnostic aid in this age group since other laboratory aids such as anti-dsDNA, ANF are often absent[18]. Other series, however had reported quite the opposite i.e. antibodies tend to decrease in the older age group[24,25]. In our study there was no significance difference in terms of prevalance of anti-Ro and anti-La between the groups. The presence of anti-Ro and anti-La together in the serum of SLE patients is rarely associated with clinically significant renal disease[18]. In contrast to other series[24] there was no increased prevalence of anti-Sm nor of antiphospholipid antibodies among our late onset SLE patients[24,27].

The explanation for the apparent age related variability in expression of the disease is still not certain. It could be related to differences in genetic predisposition, changes in immune system response with age[18,28], the influence of sex hormones and environmental factors.

We thus conclude that late-onset SLE patients form a distinct subgroup of the lupus population with benign course and have a favourable prognosis.

References

1. Kaposi MK. Neve Beitrage zur Kentiss des Lupus Erythematosus. Archiv von Dermatologie Sypilioque 1872;4 : 36-47.

2. Hargraves MM. Presentation of two marrow elements the "tart" cell and the "LE" cells. Proc Mayo Clinic 1948;23 : 25-8.

3. Ginzler EM, Schorn K. Outcome and Prognosis in Systemic Lupus Erythematosus. Rheumatic Disease Clinics of North America 1988;14 : 67-78.

4. Tan EM, Cohen AS, Fries JF, *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25 : 1271-7.

5. Hochberg MC, Boyd RE, Ahearn JH. Systemic lupus erythematosus: a review of clinico-laboratory features and immunogenetic markers in 150 patients with emphasis on demographic subsets. Medicine 1985;64 : 285-9.

6. Kellum RE, Haserick JR: a statistical evaluation of mortality based on a consecutive series of 299 patients. Arch Int Med 1964;113 : 200-10.

7. Urowitz MB. Systemic lupus erythematosus. QJM 1977;46 : 1-8.

8. Estes D, Christian CL. The natural history systemic lupus erythematosus by prospective analysis. Medicine 1971;50 : 85-104.

9. Ropes MC. Systemic lupus erythematosus: Cambridge University Press. 1976.

10. Harvey AM, Shulman LE, Timulty PA, *et al.* Systemic lupus erythematosus: a review of literature and clinical analysis of 138 cases. Medicine 1954;33 : 291-312.

11. Fries JF, Weyl S, Holman HR. Estimating prognosis in systemic lupus erythematosus. Am J Med 1974;57 : 561-72.

12. Joseph RR, Zarofenitis CJD. Clinical onset of systemic lupus erythematosus in older age group. J Am Geriat 1964;12 : 787-96.

13. Stuart BB. Late onset systemic lupus erythematosus. Am J Med 1979;66 : 722-32.

14. Baker SB, Rovira JR, Campion GV, *et al.* Late onset systemic lupus erythematosus. Am J Med 1979;66 : 727-32.

15. Foad BSI, Sheon RP, Kirsner AB. Systemic lupus erythematosus in the elderly. Arch Int Med 1972;130 : 743-6.

16. Wilson HA, Hamilton ME, Spyker DA *et al.* Age influences the clinical and serological expression of systemic lupus erythematosus. Arthritis Rheum 1981;24 : 1230-5.

17. Ballou SP, Khan MA, Kushner I. Clinical features of systemic lupus erythematosus: differences related to race and age of onset. Arthritis Rheum 1982;25 : 55-60.

18. Cotoggio LJ, Skinner RP, Smith G, *et al.* Systemic lupus erythematosus in the elderly: clinical ND serological characteristics. J Rheumatol 1984;11 : 175-81.

19. Maddison PJ. Systemic lupus erythematosus in the elderly. J Rheumatol 1987;14 : 182-7.

20. Hashimoto H, Tsuda H, Hirano T, *et al.* Difference in clinical and immunological findings of systemic lupus erythematosus related to age. J Rheumatol 1987;14 : 497-501.

21. Jonsson H, Nived O, Sturfelt G. The effect of age in unselected patients with systemic lupus erythematosus. J Rheumatol 1988;14 : 505-9.

22. Urowitz MB, Steven MB, Shulman LE. The influence of age in the clinical pattern of systemic lupus erythematosus. Arthritis Rheum 1967;10 : 319-20.

23. Mc Combs PR, Patterson JF. Factors influencing the course and prognosis of systemic lupus erythematosus. New Engl J Med 1959;260 : 1195-206.

24. Font J, Pallares L, Cervera R, *et al.* Systemic lupus erythematosus in the elderly: clinical and immunological characteristics. Ann Rheum Dis 1991;50 : 702-5.

25. Baer AN, Pincus T. Occult systemic lupus erythematosus in elderly men. JAMA 1983;249 : 3350-2.

26. Bell DA, Rigby R, Stiller CR, *et al.* HLA antigens in systemic lupus erythematosus: relationship to disease severity, age at onset, and sex. J Rheumatol 1984;11 : 475-9.

27. Manoussakis MN, Tzioufas AG, Silis MP, *et al.* High prevalence of anticardiolipin and other autoantibodies in a healthy elderly population. Clin Exp Immunol 1987;69 : 557-65.

28. Bell DA *et al.* Systemic lupus erythematosus in the elderly: Is it systemic lupus erythematosus or systemic Sjogren's syndrome? J Rheumatol 1988;15 : 723-4.

29. Grigor R, Edmond DH, Weiner M, *et al.* Systemic lupus erythematosus. Ann Rheum Dis 1978;37 : 121-8.

30. Feinglass EJ, Armett FC, Dorsch CA, *et al.* Systemic lupus erythematosus: diagnosis, clinical spectrum and relationship to other features of the disease. Medicine 1976;55 : 323-33.