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Systemic Lupus Erythematosus in the Elderly

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SUMMARY

Background: Systemic lupus erythematosus (SLE) is a multisystem inflammatory disease predominantly occurring in females of childbearing age. Late onset SLE patients are uncommon and have different clinical and laboratory characteristics compared with younger patients.

Methods: For further investigation of this subgroup, we retrospectively reviewed and analyzed 19 SLE patients with disease onset at age 60 years or older (Group A) collected from 1998 to 2008 in the computerized database of outpatients and inpatients of our hospital. For comparison, 50 SLE patients with disease onset between 15 and 40 years (Group B) were also selected using a simple random sampling method during the same period from the same database.

Results: When compared with Group B, Group A had: (1) a decreased ratio of female to male; (2) a longer lag time from disease onset to diagnosis; (3) higher rates of renal insufficiency and mortality; and (4) lower immunologic disorder rates, including anti-double-stranded DNA antibody, anti-ribonucleoprotein antibody and hypocomplementemia. The main cause of death in both groups was septic shock.

Conclusion: The clinical and laboratory features were found to be different between Groups A and B. Late onset SLE patients had a more insidious onset, a longer lag time from disease onset to diagnosis and, therefore, a higher mortality rate. Thus, this particular subgroup of SLE patients should be afforded greater attention to avoid delays in diagnosis or misdiagnosis. [International Journal of Gerontology 2009; 3(2): 108–113]

Key Words: age of onset, elderly, late onset disorders, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a multisystem disease caused by antibody production and complement fixing immune complex deposition that results in tissue damage. As many different antibodies can be produced in SLE patients, different organ-specific targets of these antibodies can cause a wide spectrum of clinical presentations, which are characterized by remissions and exacerbations[1]. The pathogenic immune responses are probably the result of environmental triggers acting on certain susceptible genes. Ultraviolet light and certain drugs are the only known environmental triggers identified to date[1]. Females of childbearing age have a predilection for human SLE, clearly indicating that reproductive hormones may play an important host role[2]. The hypothesis that SLE activity is influenced by reproductive hormones is supported by the findings that disease flares increase during pregnancy[3], and there is an increased risk of development of SLE in women taking postmenopausal hormone therapy[4]. The age of onset or diagnosis of most SLE patients is between 10 and 50 years old[5]. However, some investigators reported that the uncommon late onset SLE patients have some differences in clinical and laboratory features from the younger patients[6–20]. Late onset SLE has been defined as the disease onset occurring at ages older than 50, 55, 60 or 65 years[6–20]. However, some patients may not be postmenopausal before 60 years of age. Therefore, we identified late onset SLE patients with disease onset

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after 60 years of age in our hospital (Group A) and compared these with an SLE patient group with onset at 15–40 years of age (Group B), the most common period of disease onset, to determine if there are true differences between early and late onset SLE[12]. Mackay Memorial Hospital is a 1,900-bed medical center located in Taipei, Taiwan.

Materials and Methods

We retrospectively identified 19 SLE patients with disease onset at age 60 or older (Group A) from 1998 to 2008 at Mackay Memorial Hospital according to the inpatient and outpatient computerized database. For comparison, we also included 50 SLE patients with disease onset between the ages of 15 and 40 (Group B) by a simple random sampling method during the same period from the same database. Sixty-nine patients in total were analyzed in this study. All female patients were postmenopausal in Group A. All patients were Chinese, and they met at least four criteria of the 1997 American College of Rheumatology (ACR) updated criteria for classification of SLE[21]. The age at disease onset was defined as the date when the first recognizable clinical manifestations of SLE appeared. The age at the time of diagnosis was the date when the patients met at least four ACR criteria and were diagnosed as SLE by the physicians in this hospital.

In addition to the 11 criteria, fever, some significant organ involvement, and laboratory data were further used for evaluation of clinical and laboratory features of SLE. The SLE disease activity index (SLEDAI)[22] and the numbers of SLE criteria fulfilled were used for measuring the severity of disease when SLE was first diagnosed.

Laboratory assessment

Laboratory investigations included complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, liver enzymes, creatine phosphokinase, blood urea nitrogen, creatinine, electrolytes, urinalysis, daily urine total protein level, chest X-ray, electrocardiography, and several special examinations such as an echogram and computerized tomography, if needed.

Serologic tests included tests for rheumatoid factor (nephelometric method), syphilis (Venereal Disease Research Laboratory [VDRL] test), LE cell preparation, antinuclear antibody (indirect immunofluorescence method with HEp-2 cells as substrate), antibodies to double-stranded DNA (anti-dsDNA; indirect immunofluorescence with *Crithidia luciliae* as substrate, radioimmunoassay or enzyme immunoassay), complements 3 and 4 (nephelometric method), antibodies to extractable nuclear antigens (enzyme-linked immunosorbent assay [ELISA]), anticardiolipin antibody (international standardized ELISA kit), and lupus anticoagulant (kaolin clotting time and Russell viper venom test).

Statistical analysis

The data were analyzed statistically using Instat's free software (www.ssc.rdg.ac.uk). Fisher's exact test, Student's *t* test, Mann-Whitney test, and Wilcoxon rank sum test were used to analyze the significant differences. Statistical significance was defined as $p < 0.05$.

Results

Records of 19 lupus patients in Group A (disease onset at age 60 years or older) were analyzed and compared with 50 patients in Group B (disease onset, 15–40 years). The female predominance was reduced in Group A ($p = 0.032$) and the duration from disease onset to diagnosis was longer in Group A compared with Group B ($p = 0.008$) (Table 1).

The eight clinical ACR updated criteria for classification of SLE and significant organ involvement reported at the time of diagnosis are listed in Table 2. The four most frequent clinical manifestations of patients in Group A were serositis (52.6%), arthritis (47.4%), malar rash (42.1%) and nephritis (42.1%).

The incidence of renal insufficiency and mortality rate were significantly higher in Group A compared with Group B.

Listed in Table 3 are the other three laboratory ACR updated criteria and some important laboratory features not included in the ACR criteria but noted at the time of diagnosis. The severity of SLE compared between the two groups using SLEDAI and the numbers of ACR criteria are also included in Table 3. The three most frequent laboratory features in the late onset group were antinuclear antibody (100%), hematologic disorder (84.2%), and immunologic disorder (73.7%). Only the immunologic disorder rates, anti-dsDNA antibodies, hypocomplementemia and anti-ribonucleoprotein (RNP) antibodies, however, were significantly lower than in Group A. Table 4 shows that the main cause of death in both groups was septic shock.

Table 1. *Basic demographics of systemic lupus erythematosus patients related to age at onset*

	Group A (≥ 60 yr; $n = 19$)	Group B (≤ 40 yr; $n = 50$)	p*
Male	5	3	
Female	14	47	
Female/male ratio	2.8:1	15.7:1	0.032
Age at onset, mean ± SD (yr)	70.4 ± 7.1	27.2 ± 6.5	
Age at diagnosis, mean ± SD (yr)	70.9 ± 7.2	27.8 ± 5.5	
Duration from onset to diagnosis (mo)	5.9 ± 5.3	2.2 ± 2.2	0.008

**p value from Fisher's exact test and Student's t test. SD = standard deviation.*

Table 2. *Clinical manifestations of systemic lupus erythematosus patients related to age at onset**

	Group A (≥ 60 yr; $n = 19$)	Group B (≤ 40 yr; $n = 50$)	$p^{\dagger}$
Malar rash	8 (42.1)	21 (42.0)	NS
Discoid rash	0 (0.0)	5 (10.0)	NS
Photosensitivity	1 (5.3)	5 (10.0)	NS
Oral ulcer	5 (26.3)	3 (6.0)	0.032
Arthritis	9 (47.4)	27 (54.0)	NS
Serositis	10 (52.6)	14 (28.0)	NS
Pleural effusion	7 (36.8)	10 (20.0)	NS
Pericardial effusion	8 (42.1)	9 (18.0)	NS
Nephritis	8 (42.1)	22 (44.0)	NS
Renal insufficiency	8 (42.1)	2 (4.0)	< 0.001
Proteinuria	8 (42.1)	20 (40.0)	NS
Nephrotic syndrome	0 (0.0)	9 (18.0)	NS
Hemodialysis	1 (5.3)	2 (4.0)	NS
Neuropsychiatric	3 (15.8)	3 (6.0)	NS
Lupus pneumonitis	3 (15.8)	3 (6.0)	NS
Sjögren syndrome	1 (5.3)	2 (4.0)	NS
Gastrointestinal vasculitis	2 (10.5)	4 (8.0)	NS
Fever	3 (15.8)	16 (32.0)	NS
Cancer	2 (10.5)	0 (0.0)	NS
Mortality	6 (31.6)	4 (8.0)	0.022

**Data are presented as n (%); †p value from Fisher's exact test. NS = not significant.*

Discussion

Late onset SLE patients are relatively rare, as most cases of SLE are females of childbearing age[2]. The female-to-male ratio decreased in the elderly group, a finding also cited previous reports[12–20]. The female-to-male ratio was 2.8 in this study in the late onset group. It was significantly smaller than that of the younger group (15.7), and the results are in agreement with those reported previously, probably resulting from a lack of sex

Table 3. *Laboratory data of systemic lupus erythematosus (SLE) patients related to age at onset**

	Group A (≥ 60 yr; $n = 19$)	Group B (≤ 40 yr; $n = 50$)	$p^{\dagger}$
Hematologic disorders	16/19 (84.2)	45/50 (90.0)	NS
Hemolytic anemia	2/19 (10.5)	2/50 (4.0)	NS
Leukopenia	10/19 (52.6)	25/50 (50.0)	NS
Lymphopenia	15/19 (78.9)	44/50 (88.0)	NS
Thrombocytopenia	5/19 (26.3)	7/50 (14.0)	NS
Antinuclear antibody	19/19 (100)	50/50 (100)	NS
Immunologic criteria	14/19 (73.7)	49/50 (98.0)	0.005
Anti-dsDNA antibody‡	12/19 (63.2)	47/50 (94.0)	0.003
Hypocomplementemia	14/19 (73.7)	49/50 (98.0)	0.005
Anti-Sm antibody‡	2/19 (10.5)	15/46 (32.6)	NS
Anti-RNP antibody	2/18 (11.1)	21/44 (47.7)	0.009
Anti-Ro antibody	6/14 (42.9)	13/22 (59.1)	NS
Anti-La antibody	4/14 (28.6)	5/22 (22.7)	NS
LE cell	3/7 (42.9)	13/25 (52.0)	NS
VDRL test§	2/14 (14.3)	5/38 (13.2)	NS
Anticardiolipin antibody‡	1/12 (8.3)	4/22 (18.2)	NS
Lupus anticoagulant‡	2/13 (15.4)	5/33 (15.2)	NS
Rheumatoid factor	5/15 (33.3)	14/33 (42.4)	NS
SLEDAI	13.3 ± 8.2	14.1 ± 7.1	NS
SLE criteria	4.8 ± 0.8	4.9 ± 1.1	NS

**Data are presented as n (%) or mean ± standard deviation; †p value from Fisher's exact test, and Mann-Whitney and Wilcoxon rank-sum tests; ‡positive test; §false-positive test. dsDNA = double-stranded DNA; RNP = ribonucleoprotein; VDRL = Venereal Disease Research Laboratory; SLEDAI = systemic lupus erythematosus disease activity index. NS = not significant.*

Table 4. *The causes of death of systemic lupus erythematosus patients related to age at onset**

	Group A (≥ 60 yr; $n = 19$)	Group B (≤ 40 yr; $n = 50$)
Number of deaths	6	4
Septic shock	4/6 (66.7)	4/4 (100.0)
CVA†	1/6 (16.7)	0/4 (0.0)
Cancer‡	1/6 (16.7)	0/4 (0.0)

**Data are presented as n or n (%); †brainstem stroke; ‡lung cancer with bone metastasis. CVA = cerebrovascular accident.*

hormone effects which predisposed younger females to SLE. The lag time from disease onset to diagnosis was significantly longer in the elderly group compared with the younger group in this study (5.9 vs. 2.2 months), and it is consistent with many previous reports[10–16]. The authors of those studies commented that clinical manifestations in the elderly SLE patients tended to be more insidious, atypical and difficult to diagnose than in younger patients. A delay in making the correct diagnosis or a wrong diagnosis often occurred, partly because SLE was not considered to occur often in the elderly, and partly because the clinical expression of the disease differed to some extent in older patients[10]. The clinical manifestations of late onset SLE varied in previous reports and, therefore, different conclusions were drawn, probably because of racial differences[6–20]. Our study did not show significant differences in clinical features between Groups A and B, except the renal insufficiency rate, which was higher in the late onset group. These study results contradicted previous results which found that more serositis, lung involvement, Sjögren syndrome, less skin manifestations, photosensitivity, arthritis, and nephritis occurred in elderly SLE patients[23,24]. However, our results are in accordance with the report of Mak et al.[14], who reported that the clinical profile of late onset SLE did not constitute a benign subgroup of the lupus population. There may be some bias in information, selection and uncontrolled confounding

effects, such as racial differences, between this study and the previous articles.

The laboratory features of the elderly SLE patients in this study did not show significant differences from the younger patients except less immunologic criteria (anti-dsDNA antibody, hypocomplementemia, and anti-RNP antibody). This is consistent with the reports of Wilson et al.[7] and Ballou et al.[8], but contradicted a pooled meta-analysis[23] and a review article[24], which stated that there was a higher positive rate of rheumatoid factor, anti-Ro antibody and anti-La antibody in late onset SLE. A significantly higher positive rate of anti-RNP antibodies was noted in our study and in the reports of Catoggio et al.[9] and Maddison[10], but clinical correlations are still not clear. Less positive rates of anti-dsDNA antibody and hypocomplementemia in late onset SLE patients seemingly indicate a milder disease activity in our study. However, further comparison of disease severity between Groups A and B using SLEDAI and the numbers of SLE criteria did not show any significant difference. The mortality rate in this study was significantly higher in late onset SLE patients ($p=0.022$), which is similar to some previous reports[16,18,19]. The most frequent cause of death was septic shock in both groups and was mostly related to median to large doses of steroid treatment (0.5–2 mg/kg/day) or combined therapy with immunosuppressives. This is similar to that reported by Pu et al.[16] but contradicts the results reported by Bertoli et al.[19] in that cardiovascular disease is the leading cause of death in late onset SLE patients. These findings again revealed that late onset SLE is not necessarily a benign subgroup.

The limitations of our study and most of the previous reports are the sample size of rare late onset SLE patients being small and the race being different in different countries. These may have contributed to the differences in some results. More large-scale multicenter or international studies are needed for further investigation.

In conclusion, late onset SLE patients had more insidious onset, a longer lag time from disease onset to diagnosis, higher rates of renal insufficiency and mortality, lower positive rates of anti-dsDNA antibody, anti-RNP antibody and hypocomplementemia, and lower female predominance than the early onset patients. The most frequent cause of death in both groups was septic shock. Thus, this particular subgroup of SLE patients should be afforded greater attention to avoid delayed diagnosis or misdiagnosis.

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