Autoantibodies in systemic lupus erythematosus of late onset[1]

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Systemic lupus erythematosus (SLE) of late onset (>50 yrs) was investigated in 40 patients. The most frequent clinical manifestations involved the joints, pleura, and skin, with the kidney and central nervous system being relatively unaffected. The most common laboratory findings were antinuclear antibody and leukopenia. Nine patients (22%) had anti-DNA antibodies. Antibodies against extractable nuclear antigens (ENA) were examined in 14 patients and found to be positive in 5 (36%). Altogether, anti-DNA was present in 58% of cases ($P < 0.0002$) and anti-ENA in 72% ($P < 0.01$). The low incidence of autoantibodies correlates with the good prognosis of SLE in older patients reported in the literature.

Index terms: Autoantibodies • Lupus erythematosus

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In recent years there has been increasing interest in separating systemic lupus erythematosus (SLE) patients into subgroups according to age, race, and clinical or laboratory manifestations.[1] Several reports have noted that in older patients SLE is more benign, with a relatively high incidence of pleurisy and a relatively low mortality rate.[2–7] In addition, various reports have demonstrated the frequency of antibodies to extractable nuclear antigens (ENA) in SLE patients of unspecified age,[8–10] a finding that may have clinical predictive value. We have studied the clinical and laboratory characteristics of a group of patients with late-onset SLE, as well as the frequency of various antibodies to ENA in a subset of this group as compared to the general SLE population.

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Table 1. Clinical manifestations in late-onset SLE (N = 40)

	No. of patients
Arthritis	25 (62.5%)
Pleuritis	17 (42.5%)
Arthralgia	15 (37.5%)
Skin rash	15 (37.5%)
Constitutional syndrome	13 (32.5%)
Nephritis	10 (25%)
Pulmonary symptoms	10 (25%)
Neuropsychiatric problems	9 (22.5%)
Butterfly rash	8 (20%)
Raynaud's phenomenon	6 (15%)
Photosensitivity	5 (12.5%)
Vasculitis	4 (10%)
Alopecia	3 (7.5%)
Hepatic symptoms	3 (7.5%)
Pericarditis	3 (7.5%)
Adenopathy	2 (5%)
Mouth ulcers	2 (5%)
Discoid lupus	1 (2.5%)
Gastrointestinal symptoms	1 (2.5%)

Materials and methods

Records of Cleveland Clinic patients diagnosed as having SLE were reviewed. Those who met the American Rheumatism Association criteria for SLE[11] and first had symptoms after the age of 50 were considered to have late-onset SLE. Patients whose SLE was diagnosed after the age of 50 but had had symptoms prior to that time were excluded. Only those with follow-up lasting 4 years or longer were included (except for those who died during the four-year period). Patients taking drugs capable of inducing SLE were included only if they had significant levels of antibodies against native DNA, and/or their symptoms continued after medication was halted. A total of 40 patients met these criteria and constituted the study population. Anti-native DNA levels were measured by a modification of the Farr assay.[12] The labeled DNA was passed through a Millipore filter to assure double-strandedness. Anti-ENA was assayed in two steps. In the screening step, sera were tested for precipitation lines in 0.6% agarose gel against an aqueous extract of rabbit thymus.[13,14] In the identification step, positive sera were examined against rabbit thymus extract in wells adjacent to sera of known specificity. Identifiable specificities included ribonucleoprotein (RNP), Sm, and SS-B (La, HA). The chi-square test was used for statistical analysis.

Table 2. Laboratory manifestations in late-onset SLE (N = 40)

	No. of patients
ANA	40 (100%)
Leukopenia	18 (45%)
Anti-ENA (N = 14)	5 (36%)
Hemolytic anemia	13 (32.5%)
High sedimentation rate	13 (32.5%)
Hyperglobulinemia	13 (32.5%)
Anti-DNA	9 (22.5%)
Rheumatoid factor	7 (17.5%)
Low complement	6 (15%)
Thrombocytopenia	5 (12.5%)
Cryoglobulins	3 (7.5%)

Results

Thirty-four women and 6 men were studied. The onset of disease was acute in 6 patients and insidious in 34. Five patients had a history of drug-induced SLE, associated with hydralazine in 2, diphenylhydantoin in 2, and procainamide in 1. The mean age at onset of initial symptoms was 57 years ± 3.3 (S.E.M.). A total of 23 patients (57.5%) was diagnosed as having SLE within a year after the onset of symptoms, 7 (17.5%) in the second year, 3 (7.5%) in the third year, 2 (5%) in the fourth year, and 5 (12.5%) up to 12 years after onset. Patients were followed up for an average of five years (never less than four years). During this period, 5 patients (12.5%) died. Three of these 5 patients had cancer, diagnosed as acute lymphocytic leukemia, carcinoma of the prostate, and cancer of the colon, respectively. The interval between onset of SLE and death was 7.0 ± 3.8 years. The most common clinical manifestations were arthritis (62.5%), pleuritis (43.5%), arthralgia (37.5%), and skin rash (37.5%), with nephritis and central nervous system abnormalities occurring less frequently (*Table 1*).

All patients had antinuclear antibodies, and 9 (22%) had anti-DNA antibodies. Leukopenia was present in 45% of patients, excluding those receiving cytotoxic therapy (*Table 2*). Anti-ENA was examined in 14 patients and was positive in 5 (36%). Three patients had anti-RNP, 1 had anti-RNP and anti-Sm, and 1 had an unidentified anti-ENA which did not develop lines of identity with sera known to be positive for anti-RNP, Sm, or SS-B. SLE-related clinical and laboratory findings were essentially similar in the 5 patients who died and those who survived. In a previous re-

port,[15] 59 out of 102 patients with SLE (58%) had antibodies to DNA and 74 (72%) had antibodies against ENA. Comparison with the present late-onset group showed that the latter patients had a significantly lower prevalence of anti-DNA ($P < 0.0002$) and anti-ENA ($P < 0.01$).

Discussion

Comparison of our results with those of Baker et al[5] and Wilson[7] reveals many similarities. The age at onset of disease was 57, compared to 59.5 in Baker's patients. The sex distribution, time of diagnosis after onset, and overall prognosis were similar in both our study and Baker's. All three studies showed frequent occurrences of arthritis and pleuritis. Wilson et al reported higher prevalences of Raynaud's phenomenon (35%), alopecia (52%), and mouth ulcers (53%). Neuropsychiatric complications occurred in 22%–29% of patients in all three studies.

Significant renal involvement was present in 25% of our patients. Wilson et al reported a similar frequency of kidney involvement and observed a decreasing likelihood of nephrotic-range proteinuria with increasing age, varying from above 40% in the younger group to below 10% in the older group. Baker et al found that 55% of their patients had nephritis; however, their criteria for nephritis were different from ours, which could account for the lower frequency of renal disease in our study. We included only patients with proteinuria >3.5 g/24 hr and/or cellular casts in the urine, while Baker et al included patients with proteinuria ≥ 1 g/24hr, microscopic hematuria or casts, and/or serum creatinine ≥ 1.5 g/100 mL.

Our laboratory findings are similar to those of Wilson et al, who reported that anti-DNA antibodies and low complement levels correlated inversely with age. In comparing our results with Baker's study, we found similar frequencies of hemolytic anemia, leukopenia, and thrombocytopenia; however, anti-DNA antibodies (22% versus 70%), elevated sedimentation rate (32% versus 93%), hypocomplementemia (15% versus 64%), and hyperglobulinemia (32% versus 77%) were less frequent in our series.

We agree with previous studies that the frequency of severe renal disease is lower in late-onset SLE compared with SLE in general. Serologic findings paralleled this difference; although our data in this population are limited, the lower frequencies of anti-native DNA (22% versus 58%), anti-ENA (36% versus 72%), and anti-Sm (7% versus 23%) correlate with this more benign prognosis. In our previous study of 102 patients with SLE,[15] nephritis was significantly more frequent in anti-ENA-positive than in anti-ENA-negative patients. Thus the lower prevalence of anti-ENA among elderly patients appears to correlate with the lower frequency of nephritis. Similarly, 48% of the 23 anti-Sm-positive patients in the earlier study had nephritis, compared with 22% of the 79 anti-Sm-negative patients. Only 1 of the 14 patients tested in the present study had anti-Sm, and she had nephritis. Of the 5 patients who died, 3 had cancer, compared with 3 out of 5 patients with late-onset SLE in Joseph's series,[2] though the significance of this possible association is unclear.

Although, on the average, late-onset SLE would appear to be milder than early-onset SLE on the basis of this and previous studies, it could merely be that patients with severe disease died at a younger age and were thus eliminated from this group. However, this is unlikely, since only patients whose *initial* symptoms occurred after 50 years of age were included.

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