THE CLINICAL SIGNIFICANCE OF RAYNAUD'S PHENOMENON IN SYSTEMIC LUPUS ERYTHEMATOSUS

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In a prospective study of 226 patients with systemic lupus erythematosus (SLE), 91 patients (40%) had Raynaud's phenomenon. These patients were compared to 135 patients without Raynaud's phenomenon. Patients with Raynaud's phenomenon had a greater incidence of arthritis ($P < 0.02$), malar rash ($P < 0.003$), and photosensitivity ($P < 0.03$), and a lesser incidence of severe renal disease as manifested by serum creatinine over 3.0 mg/dl ($P < 0.007$) or creatinine clearance below 60 ml/minute. Patients with Raynaud's phenomenon were less likely to have severe, life threatening disease and received a lower average monthly ($P < 0.01$) and a lower peak daily corticosteroid dose ($P < 0.01$). Fourteen patients (16%) with Raynaud's phenomenon died, compared to 41 without (30%) ($P < 0.03$). Raynaud's phenomenon in patients with SLE is associated with milder disease and may be regarded as a favorable prognostic sign.

Raynaud's phenomenon has been noted in about one-fifth of patients with systemic lupus erythematosus (SLE) (1,2). It has received little attention in the literature, and its clinical significance is not well known. Fries (3) suggested that SLE patients with Raynaud's phenomenon had a relatively mild renal disease and a better prognosis. The clinical manifestations, laboratory data, disease activity, corticosteroid therapy, and survival were compared in patients with and without Raynaud's phenomenon in a prospective study of patients with SLE followed at Downstate Medical Center.

PATIENTS AND METHODS

This study was a computer aided analysis of results of a prospective study on the clinical course in patients with SLE who were followed at Downstate Medical Center during a 10-year period from July 1966 through September 1976. (4). Information was recorded at the time of study entry, either on admission to the hospital or at the initial outpatient visit, and thereafter at approximately 6-month intervals. Data for all patients having at least one interval evaluation following the initial entry form were included. Data were obtained regarding

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Table 1. Activity index for each interval evaluation in SLE patients

Group	Description*
1	No signs or symptoms of SLE or normal laboratory parameters
2	No signs or symptoms of SLE; elevated ESR; positive anti-DNA; hypocomplementemia or leukopenia
3	Active arthritis; skin rash; alopecia; oral ulcerations; cutaneous vasculitis; skin ulcers; uveitis or fever
4	CNS disease; peripheral neuropathy; serositis; anemia; nephritis without uremia or continued presence of nephrotic syndrome
5	Coma; GI vasculitis; TTP-like syndrome or DIC: pulmonary hemorrhage; malignant hypertension; nephritis with uremia or appearance of nephrotic syndrome

* ESR = erythrocyte sedimentation rate; CNS = central nervous system; GI = gastrointestinal; TTP = thrombotic thrombocytopenic purpura; DIC = disseminated intravascular clotting.

medical history, symptoms, physical findings, laboratory values, and other interval events. For each interval, information was recorded regarding each specific medication received, the length of time in months it was taken, and the dose including the highest dose given during the interval, the dose at the time of interval evaluation, and the average dose during the interval. Activity index of SLE for each interval evaluation was assessed by placing the patients into five sub-groups, ranging from asymptomatic disease to life-threatening disease manifestations. Each patient was assigned to the highest numbered group which included any one feature he or she exhibited in an active or evolving form during the interval involved. (Table 1).

Included in the study were all patients who had a clinical diagnosis of SLE, according to the four diagnostic criteria of the American Rheumatism Association (ARA) (5). Excluded from the study were patients who had a diagnosis of mixed connective tissue disease or scleroderma, skin changes consistent with scleroderma, or antibodies to ribonucleoprotein (RNP) at any time during the course of their disease. Of the 91 remaining patients with Raynaud's phenomenon included in the study, 65 had one or more of the following: 21 had a diffuse proliferative glomerulonephritis, 20 had antibodies to DNA, 9 had antibodies to Sm, and 18 had negative test results for antibodies to extractable nuclear antibodies (ENA), thus excluding the possibility of MCTD in these patients.

Table 2. Raynaud's phenomenon in 226 patients with systemic lupus erythematosus

	Raynaud's	No Raynaud's
Number of patients	91	135
Female	89	124
Male	2	11
Mean age		
At first SLE symptom	25	28
At SLE diagnosis	27	30
Race (number)		
Black (142)	45	97
White (52)	25	27
Hispanic (29)	20	9
Oriental (3)	1	2

Table 3. Joint and skin manifestations in SLE patients with and without Raynaud's phenomenon

Symptom	% Raynaud's	% no Raynaud's*
Objective arthritis	66	48 ($P < 0.02$)
Malar rash	75	54 ($P < 0.003$)
Photosensitivity	22	10 ($P < 0.03$)
Cutaneous vasculitis	26	15 (NS)
Oral ulcers	18	12 (NS)
Alopecia	67	64
Discoid lupus	24	24
Aseptic necrosis	9	10

* NS = not significant.

The diagnosis of Raynaud's phenomenon required at least a two-phase color reaction and bilateral involvement by patient's history or physician's observation (5,6). Data were analyzed by computer from study entry to the time of last followup visit or death. Patients with Raynaud's phenomenon were compared to patients who did not have Raynaud's phenomenon. Statistical analysis was done by Student's t test and by Chi-square with Yates correction (7).

RESULTS

Two hundred twenty-six patients with SLE who were followed for an average of 46 months (range: 2–141 months) were included in this study. Ninety-one (40%) had Raynaud's phenomenon; 58 patients (64%) had Raynaud's phenomenon on their first interval evaluation, and an additional 33 (36%) developed it sub-

Table 4. Renal disease in SLE patients with and without Raynaud's phenomenon

	% Raynaud's	% no Raynaud's
Serum creatinine over 3.0 mg/dl	11	27 ($P < 0.007$)
Creatinine clearance below 60 ml/minute	34	48 ($P < 0.06$)
Proteinuria over 3.5 gm/24 hours	10	14
Cellular casts in urine	32	34
Dialysis	2	4
Pathology*		
Diffuse proliferative nephritis	35	46
Membranous nephritis	15	14
Focal nephritis	33	22
Mesangial nephritis	11	11
Normal	6	7

* % in 109 patients who had biopsies.

Table 5. Laboratory parameters in SLE patients with and without Raynaud's phenomenon

	% Raynaud's	% no Raynaud's
LE cells	57	64
False positive VDRL	14	16
Leukopenia	21	24
Thrombocytopenia	13	14
Hemolytic anemia	14	18
Hypocomplementemia	52	47
Rheumatoid factor	25	15

sequently. The age, sex, and race of the patients are compared in Table 2. The female to male ratio was not different between patients with and without Raynaud's phenomenon. Patients with Raynaud's phenomenon tended to be younger, but not significantly so. Raynaud's phenomenon occurred in one-third of the black patients, half of the white patients, and two-thirds of the hispanic patients. Forty-nine percent of the patients with Raynaud's phenomenon were black, while 72% of the patients without Raynaud's phenomenon were black ($P < 0.002$). Objective arthritis occurred in 60 patients (66%) with Raynaud's phenomenon and 65 (48%) patients without ($P < 0.02$) (Table 3). Malar rash occurred in 68 (75%) patients with and 73 (54%) patients without Raynaud's phenomenon ($P < 0.003$). Photosensitivity occurred in 20 (22%) patients with and 13 (10%) patients without Raynaud's phenomenon ($P < 0.03$). Other skin manifestations including cutaneous vasculitis, oral ulcers, alopecia, and discoid lupus were not different between the two groups. Aseptic necrosis of bone occurred in 8 (9%) patients with and 14 (10%) patients without Raynaud's phenomenon. Pleuritis and/or pericarditis occurred in 61 (67%) of patients with and 103 (76%) of patients without Raynaud's. Central nervous system disease occurred in 43 (47%) patients with and 60 (44%) without Raynaud's. Myositis occurred in 8 (9%) patients with and 12 (9%) patients without Raynaud's. Lung disease occurred in 6 (7%) patients with and 7 (5%) patients without Raynaud's.

Renal disease was equal in prevalence in patients with and without Raynaud's phenomenon. However, severe renal disease, as indicated by serum creatinine over 3.0 mg/dl was less common in patients with Raynaud's phenomenon (11%), compared to patients without (27%) ($P < 0.007$) (Table 4). Creatinine clearance below 60 ml/minute was found in 31 (34%) patients with and 65 (48%) patients without Raynaud's phenomenon, ($P < 0.06$). There was no difference between the groups in the incidence of severe proteinuria (over 3.5 gm/24 hours) or the pathologic classification in patients who had renal biopsies. The incidence of positive LE cell test, biologic false positive VDRL, leukopenia, thrombocytopenia, hemolytic anemia, hypocomplementemia, and positive rheumatoid factor was not different between the two groups (Table 5).

The mean number of ARA criteria fulfilled at study entry by patients with Raynaud's phenomenon was 5.1 compared to 4.4 fulfilled by patients without Raynaud's. The mean number of criteria fulfilled at any time was 6.5 in patients with and 5.3 in patients without Raynaud's. (These differences were not significant.)

Activity index for each interval evaluation was done by placing the patients in subgroups according to their activity ranging from nonactivity (group 1) to life-threatening disease manifestation (group 5). The activity index assessment for the first and last interval evaluation is presented in Table 6. The distribution of patients with and without Raynaud's phenomenon is similar in groups 1 through 4. However, there were significantly fewer patients with Raynaud's phenomenon in group 5 ($P < 0.05$), both at first and last interval evaluation.

Table 7 presents duration and dose of corticosteroid therapy in patients with and without Raynaud's phenomenon. The percentage of patients who received corticosteroid therapy before study entry and during followup was similar in the two groups. Patients with Raynaud's phenomenon had longer mean followup (mean of 53 months compared to 41 months in patients

Table 6. Assessment of activity in SLE patients with and without Raynaud's phenomenon

	First interval		Last interval	
Activity index	% Raynaud's	% no Raynaud's	% Raynaud's	% no Raynaud's
Group 1	1	0	2	6
Group 2	2	2	8	12
Group 3	31	27	28	21
Group 4	53	44	53	41
Group 5 ($P < 0.05$)	13	26	9	20

Table 7. Corticosteroid therapy in SLE patients with and without Raynaud's phenomenon

	Raynaud's	No Raynaud's
Corticosteroids before study entry, % patients	63%	62%
Corticosteroids during study period, % patients	87%	77%
Mean duration of followup	53 months	41 months
Mean duration of corticosteroid therapy*	31 months	22 months
Average monthly corticosteroid dose*	0.7 gm	1.2 gm ($P < 0.01$)
Mean highest daily corticosteroid dose*	52 mg	84 mg ($P < 0.01$)

* Patients receiving no corticosteroids were not included in the average.

without Raynaud's), and these patients received corticosteroids for a longer period of time (mean 31 months compared to 22 months in patients without Raynaud's) ($P < 0.03$). The average monthly corticosteroid dose was significantly lower (0.7 gm) in patients with Raynaud's phenomenon ($P < 0.01$). The mean highest daily corticosteroid dose was also significantly lower in patients with Raynaud's phenomenon (mean 52 mg compared to 84 mg) ($P < 0.01$).

Fifty-five patients died during the followup period: 14 (16%) of the patients with Raynaud's phenomenon and 41 (30%) without Raynaud's phenomenon died ($P < 0.03$). The highest mortality occurred during the first year of followup.

DISCUSSION

SLE appears to be milder on the average in patients with Raynaud's phenomenon. In our patients, Raynaud's phenomenon was associated with arthritis, malar rash, and photosensitivity, generally milder manifestations of SLE. Severe renal disease as manifested by elevated serum creatinine and lower creatinine clearance was less common in patients with Raynaud's phenomenon. Fewer patients with Raynaud's phenomenon were in the group with the highest activity index. Patients with Raynaud's phenomenon had a significantly lesser highest daily and average monthly corticosteroid dose, consistent with milder disease or a better response to corticosteroids. Finally, mortality in patients with Raynaud's phenomenon was significantly lower. Fries and Holman found no significant association between Raynaud's phenomenon and either arthritis or skin rash, but our data confirm their impression of the presence of less severe renal disease and a better prognosis in SLE patients with Raynaud's phenomenon (3).

The paucity of Raynaud's phenomenon among our black compared to white patients is of interest, in view of suggestions by Siegel and Lee (8) of significantly higher mortality in black patients with SLE. Others, however, failed to detect a relationship between race and mortality or disease severity (1,9).

Recently, Winn and co-workers (10) found that SLE patients with Sm antibodies had a more benign course with milder renal disease. Raynaud's phenomenon occurred in a significantly higher percentage of patients with Sm. Fries found an increased incidence of antibodies to ENA in patients with Raynaud's phenomenon (3). It is therefore possible that the milder clinical disease found in patients with Raynaud's phenomenon is due to a protective effect of an antibody, perhaps Sm, associated with this phenomenon.

Raynaud's phenomenon is regarded as an early manifestation in SLE (3) and may antedate other manifestations by years (6). However, one-third of our patients developed Raynaud's phenomenon later in the course of their disease. Although Raynaud's phenomenon was associated with milder ARA criteria, such as arthritis, malar rash, and photosensitivity, the mean number of ARA criteria fulfilled by patients with Raynaud's phenomenon was slightly higher than in patients without Raynaud's. We were unable to confirm previous reports suggesting an excess of Raynaud's phenomenon in SLE patients with aseptic necrosis of bone (11,12).

In summary, Raynaud's phenomenon in our SLE patients was less common in blacks and was associated with a higher incidence of arthritis, malar rash, and photosensitivity, milder renal disease, lower requirement and possibly better response to corticosteroids, and better survival. The presence of Raynaud's phenomenon in patients in SLE may be regarded as a good prognostic sign.

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