Clonal T Cells in the Blood of Patients With Systemic Sclerosis

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Background: It has been suggested that clonal T cells may play a critical role in the pathogenesis of systemic sclerosis.

Observations: A monoclonal population of T cells was found in blood samples from 13 (34%) of 38 consecutive patients with a definite diagnosis of systemic sclerosis who were prospectively examined by T-cell receptor \( \gamma \) gene rearrangement using polymerase chain reaction and denaturating gradient gel electrophoresis. In the healthy control group, the same type of examination revealed a monoclonal population of T cells in the blood samples from only 3 healthy subjects (4%) (odds ratio, 12.28; 95% confidence interval, 2.76-54.64; \( P = .001 \)). Patients who had a circulating clonal population of T cells were older than those who did not (67 years vs 48 years; \( P = .04 \)). There was a marked relationship between systemic sclerosis subtypes and the presence of a circulating clonal population of T cells. Twelve (43%) of 28 patients with limited cutaneous sclerosis exhibited a circulating clonal population of T cells, whereas only 1 (10%) of the 10 patients with diffuse cutaneous sclerosis had evidence of T-cell clonality (\( P < .01 \)).

Conclusions: Clonally expanded T cells were more commonly detected in patients with limited cutaneous sclerosis than in those with diffuse cutaneous sclerosis, which is also in accordance with a possible role of clonal T cells in patients with limited cutaneous sclerosis.

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In a prospective study, French et al found that clonal T cells are frequently detected in peripheral blood samples from patients with systemic sclerosis (SSc). In their series, expanded clonal T cells were found in 6 (46%) of 13 peripheral blood samples from patients with SSc, whereas no clonal T cells were found in the control group. The authors suggested that clonal T cells may play a critical role in the pathogenesis of SSc. These data prompted us to conduct a prospective study (1) to evaluate the prevalence of a T-cell clonal population in peripheral blood samples from patients with SSc and (2) to determine a possible relationship between both clinical and biological parameters of patients with SSc and the presence of a T-cell clonal population in peripheral blood samples.

Methods

Blood samples were obtained from all patients, and peripheral blood mononuclear cells were immediately isolated from whole blood using the Ficoll-Hypaque technique. Analysis of T-cell receptor \( \gamma \) gene rearrangement using polymerase chain reaction and denaturating gradient gel electrophoresis (TCR-\( \gamma \) PCR DGGE) was performed as previously described.

Thirty-eight consecutive patients with a definite diagnosis of SSc were included in the study. The criteria for the diagnosis of SSc were based on the American College of Rheumatology criteria. All patients were seen at the University of Rouen Medical Center, Rouen, France, between 2001 and 2002. There were 6 men and 32 women, with a median age of 54 years (age range, 26-87 years); the median duration of the disease, considered to have existed from the onset of the Raynaud phenomenon, was 55 months (range, 8-432 months). Patients were classified according to the criteria of Leroy et al: 10 patients (26%) had diffuse cutaneous SSc (dcSSc) and 28 (74%) had limited cutaneous SSc (lcSSc).

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The findings of TCR-\( \gamma \) PCR DGGE of the blood samples from patients with SSc were compared with those from 76 age- and sex-matched healthy subjects (12 men and 64 women; median age, 57 years; age range, 29-89 years). For each patient, we attempted to select 2 same-sex control subjects whose age was within 5 years of the patient’s age. None of the patients with SSc or the control subjects had a history of other connective tissue disorders or hematologic diseases (eg, lymphoma, cutaneous T-cell lymphoma, or T-cell leukemias).

Statistical analyses were performed using commercially available software (Version 8.0; Stata Corp, College Station, Tex). For group com-
parisons of binary data, we used either the χ² test or the Fisher exact test, depending on the sample size; for comparisons of continuous data, we used the Mann-Whitney test. The results were regarded as significant at P<.05. For comparisons of patients with SSC and control subjects, conditional logistic regression was also performed, and matched odds ratios (ORs) with their 95% confidence intervals (CIs) were calculated.

RESULTS

PREVALENCE OF BLOOD T-CELL CLONALITY

Using TCR-γ PCR DGGE, a monoclonal population of T cells was detected in blood samples from 13 (34%) of 38 consecutive patients with SSC. In the healthy control group, TCR-γ PCR DGGE revealed a monoclonal population of T cells in blood samples from only 3 subjects (4%) (OR, 12.28; 95% CI, 2.76-54.64; P = .001).

FACTORS ASSOCIATED WITH A T-CELL CLONAL POPULATION

Patients with SSC who had a circulating clonal population of T cells were older than those who did not (67 years vs 48 years; P = .04). Among female patients, a history of pregnancy was similar in patients with and without clonal T cells (71% vs 62%; P>.99).

The median duration of SSC was significantly longer in patients with a T-cell clonality than in those without (78 months vs 36 months; P = .91). Moreover, we were able to demonstrate a marked relationship between SSC subtypes and the presence of a circulating clonal population of T cells: 12 (43%) of the 28 patients with lcSSc had a circulating clonal population of T cells, whereas only 1 (10%) of the 10 patients with dcSSc had evidence of T-cell clonality (P<.01).

The prevalence of the following systemic manifestations related to SSC was similar in patients with and without a circulating clonal population of T cells: (1) pitting scars (54% vs 56%; P>.99); (2) esophageal involvement characterized by motor disturbances on esophageal manometry (91% vs 72%; P>.99); (3) interstitial lung disease defined on computed tomograms by bilateral shadowing associated with pulmonary function test abnormalities manifested by restrictive changes (ie, vital capacity, <80%) and a diffusing capacity for carbon monoxide of less than 70% predicted (23% vs 12%; P = .39); (4) articular dysfunction (46% vs 40%; P = .74); and (5) renal crisis (0% vs 8%; P = .53). We also failed to find a significant difference in the degree of SSC severity between patients with and without a circulating clonal population of T cells (4 vs 4; P = .20).

Finally, no differences were found in the following laboratory values between patients with SSC who had a circulating clonal population of T cells and those who did not: erythrocyte sedimentation rate, 18 mm/h vs 12 mm/h (P = .35); C-reactive protein, 3 mg/L vs 3 mg/L; (P = .35); hemoglobin, 12.9 g/dL vs 13.0 g/dL (8.0 mmol/L vs 8.1 mmol/L) (P = .71); serum urea nitrogen, 15.4 mg/dL vs 14.0 mg/dL (5.5 mmol/L vs 5.0 mmol/L; P = .03). The frequency of anti–Scl-70 antibodies (8% vs 24%; P = .38) and anticentromere antibodies (46% vs 36%; P = .54) was also similar in the 2 groups, respectively.

Although clonality of T cells is more commonly encountered in diseases involving T-cell lineage (eg, cutaneous T-cell lymphoma and T-cell leukemias), it may be associated with other conditions, including autoimmune disorders such as rheumatoid arthritis, as well. Our study also demonstrated a marked frequency (34%) of clonally expanded T cells in the peripheral blood samples from patients with SSC compared with the general population. Our findings therefore confirm the data of previous authors who have observed clonal T-cell populations in samples of blood and numerous organs (eg, skin and lungs) of 20% to 56% patients with SSC.

Previous authors have also suggested that clonal populations of T cells may have a role in the pathogenesis of SSC. In essence, in a recent series, French et al showed that patients with SSC who have detectable expanded clonal T-cell populations in samples of peripheral blood appear more likely to respond to extracorporeal photophoresis. They postulated that these findings reinforce the theory that clonal T cells may be involved in the pathogenesis of SSC, as extracorporeal photophoresis has been reported to be an efficacious therapy in patients with other T-cell disorders, such as the Sézary syndrome (ie, the leukemic form of cutaneous T-cell lymphoma). In our population, no patient underwent photophoresis. In the present study, the demonstration that clonally expanded T cells were more commonly detected in patients with lcSSc than in those with dcSSc is also in accordance with a possible role of clonal T cells in patients with lcSSc. To date, however, the pathogenic properties of these clonal T cells have not been clearly shown in SSC. Finally, it is of interest to note that the presence of clonally expanded T cells in the peripheral blood samples in our study could not be considered as a predictive factor of organ involvement severity in patients with SSC.

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REFERENCES