Autoantibodies in Patients with Systemic Sclerosis and Cancer: A Case-Control Study

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ABSTRACT. ***Objective.*** To determine the prevalence of specific autoantibodies in a cohort of patients with systemic sclerosis (SSc) and a diagnosis of cancer, and to compare it to that in a group of patients with SSc who were never diagnosed with cancer.

Methods. From 769 patients with SSc followed at our center over the past 15 years, 77 had a diagnosis of cancer. The results of autoantibody studies in this group were compared to those from 159 SSc patients without cancer randomly selected from the rest of the patient population using chi-square test for independence and the null hypothesis for 2 population proportions.

Results. There was no statistically significant difference between the proportions of patients with positive autoantibodies between the 2 groups, except that a higher prevalence of autoantibodies with a nucleolar immunofluorescence pattern was observed in the group of patients who were never diagnosed with cancer ($p < 0.01$).

Conclusion. In contrast to previous studies, in our case-control study we were not able to detect a significant difference in autoantibody frequency or patterns among SSc patients with and without a diagnosis of cancer. These results refute the conclusion made previously that certain autoantibodies may represent risk factors for the development of cancer in patients with SSc. (J Rheumatol 2003;30:1994–6)

Key Indexing Terms:
SYSTEMIC SCLEROSIS AUTOANTIBODIES CANCER
ANTITOPOISOMERASE ANTICENTROMERE

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder characterized by a pathologic triad comprising severe and often progressive tissue fibrosis with excessive collagen deposition in affected organs, alterations in the microvasculature, and cellular and humoral abnormalities[1,2]. Several studies have described an increased frequency of cancer in patients with SSc, an association that contributes to an increased mortality[3-7]. The increased frequency of lung cancer in patients with SSc was considered to be a consequence of lung fibrosis; however, SSc often follows or has simultaneous onset with lung cancer[8], an observation that does not support this view. An increased frequency of cancer in first-degree relatives of patients with SSc has been described[9], although it is not clear whether this is due to genetic factors or to shared environmental influences among family members. Four studies with very small numbers of patients with SSc and cancer examined the association between autoantibodies and cancer[10-13]. Two studies found that Scl-70 autoantibodies were increased in frequency in patients with cancer[10,11], whereas another study showed a high frequency of neoplasia in patients with anticentromere antibodies[12]. Finally, a study from France showed that all 3 lung cancer cases in their cohort had antibodies to centromere proteins[13].

To examine this hypothesis, we performed a case-control study in a large cohort of patients with SSc followed at our institution since 1987 to examine whether the autoantibody profile in patients with SSc is a risk factor for development of cancer, and to determine whether any particular type of malignancy is associated with a particular autoantibody profile.

MATERIALS AND METHODS

The records of all patients with SSc followed at the Scleroderma Center of Thomas Jefferson University over the past 15 years were reviewed. All patients fulfilled the American College of Rheumatology criteria for the classification of SSc[14]. From this cohort all patients who had been diagnosed with a malignancy were identified by review of medical records and pathology reports, or by communication with referring physicians. Cases of skin cancer were excluded. For a comparison cohort, 150 SSc patients who had not been diagnosed with a malignancy at the time of this study were selected randomly. Demographic data were recorded for all patients, and for the purposes of this study all autoantibody results were recorded for each patient to be included in the analysis. Antinuclear (ANA) and anticentromere antibodies (ACA) were detected by immunofluorescence on

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Supported by NIH Grant AR19616 (Dr. Jimenez) and NIH Training Grant AR07583 (Dr. Derk).

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Submitted December 24, 2002; revision accepted February 14, 2003.

HEp-2 cells. Anti-Scl-70 was detected by ELISA. Quantitative data were evaluated as a mean with a 95% confidence interval. Qualitative data were evaluated as a percentage of the total. Statistical analyses were carried out with the chi-square test for independence and Student's t test where indicated. In cases where the central limit theorem applied, a normal distribution was assumed and the null hypothesis of 2 proportions being equal was tested by referring to tables of normal distribution. Statistical significance was indicated at the $\alpha = 0.05$ level.

RESULTS

Seven hundred sixty-nine patients diagnosed with either diffuse or limited SSc were followed at the Scleroderma Center over the past 15 years, with a total followup of 3775 patient-years. From this cohort, 77 patients were diagnosed with a malignancy other than skin cancer. From the 692 SSc patients who had never been diagnosed with a malignancy, 150 were randomly selected for a control group. Demographic data for the 2 groups were similar, except for a statistically significant difference between the mean ages at diagnosis of SSc (Table 1). This difference could be accounted for by the higher expected prevalence of malignancy in older patients.

There was no statistically significant difference in the frequency of antibodies to topoisomerase I between the 2 groups either by comparison of 2 proportions ($p = 0.44$) or by the chi-square test for dependence (chi-square = 0.55, odds ratio = 0.73). The same evaluation performed for ACA also showed no significant difference between the 2 groups ($p = 0.23$, chi-square = 1.4, OR = 0.66). A comparison of the frequency of a pattern consisting of ANA(+), anti-Scl-70(–), and ACA (–) results among the 2 groups also showed no statistically significant difference ($p = 0.54$, chi-square = 0.42, OR = 0.83). However, analysis of the ANA immunofluorescence patterns showed that patients who did not have a diagnosis of malignancy had a significantly higher frequency of autoantibodies with a nucleolar pattern compared to patients who had a diagnosis of malignancy ($p < 0.01$) (Table 2). Finally, a statistically significant excess of ANA titers > 1:640 was noted among the patients diagnosed with cancer (Table 2).

Autoantibody patterns in relation to selected cancer sites were also examined (Table 3), although owing to the small number of cases in each group, no valid statistical analyses could be performed. Of interest, all patients who were diagnosed with non-Hodgkin's lymphoma, 57.1% of patients with SSc and oropharyngeal malignancies, and 57.1% of patients with esophageal cancer displayed the pattern of ANA(+), anti-Scl-70(–), and ACA (–), whereas only 25% of patients with ovarian and 39.1% of patients with breast carcinoma had this pattern of autoantibodies. Another result of note was that only 65% of patients with breast cancer and 50% of patients with ovarian cancer were ANA(+), compared to > 90% positivity observed in large epidemiological studies of patients with SSc[1].

DISCUSSION

A link between malignant neoplasms and SSc was strongly suggested by several large epidemiological studies[3-7]. More recent studies have attempted to link cancer in patients with SSc to the presence of either antitopoisomerase I or ACA[10–13]. The purpose of this case-control study was to either replicate and confirm or contradict these previous results. Using a case-control model, we were unable to reproduce these previous results employing a controlled statistical analysis. The results we obtained showed no significant difference in the frequency of autoantibodies among SSc patients who have cancer and those who do not. These observations contradict the previous suggestions that specific autoantibodies in patients with SSc may be a risk factor for the development of cancer[10-13].

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Table 1. Selected demographic and clinical data in SSc patients with and without cancer.

	Cancer Patients, n = 77	Patients without Cancer, n = 150	p
Age at diagnosis of SSc, yrs	50.1 ± 3.39	44.3 ± 2.4	< 0.01
Female, %	78	83.30	0.35
Race, %			
Caucasian	84	84	1.0
African American	12	12.60	0.89
Hispanic	1	3.4	
Oriental	3	0	
Years of followup	6.8 ± 1.5	5.9 ± 0.9	> 0.2
Clinical subset of SSc, %			
Diffuse	58.40	48.60	0.16
Limited	41.60	51.40	0.16

Table 2. Autoantibodies and cancer in SSc patients. Data are given as percentages.

Autoantibody Studies	SSc + Cancer, n = 73*	SSc, No Cancer, n = 150	p
ANA (+)	86	90.60	0.35
ANA titer (> 1:640)	73	61.30	0.05
ANA pattern			
Homogeneous	22	20	0.85
Speckled	52	44	0.25
Nucleolar	16	34	< 0.01
Centromere	15	19.30	0.42
Anti-Scl-70 (+)	12.50	15.30	0.44
Anticentromere (+)	20.50	26.60	0.23
ANA (+), Scl-70 (–), ACA (–)	47.90	50.00	0.54

* 4 patients in the SSc + cancer group did not have available autoantibody studies.

Table 3. Autoantibody patterns in SSc patients with cancer according to selected cancer sites. Data are given as percentages.

Cancer Site (no. of patients)	Anti-Scl-70 (+)	Anticentromere (+)	ANA (+), Scl-70 (–), ACA (–)	ANA (+)
Breast (23)*	4	26	39.10	65
Lung (10)	30	30	40	100
Oropharynx (7)**	15	0	57.10	86
Esophageal (7)	14.70	28.50	57.10	100
Non-Hodgkin's lymphoma (5)***	0	0	100	100
Ovarian (4)	0	25	25	50

* One patient without available autoantibody studies. ** Two patients without autoantibody studies. *** One patient without autoantibody studies.

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