Clin Rheumatol (2000) 19:123–126

Clinical Rheumatology

Original Article

Anticentromere Antibody as a Risk Factor for Cancer in Patients with Systemic Sclerosis

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Abstract: This study has estimated the cancer risk among patients with systemic sclerosis (SSc) using a population-based analysis. Using the inpatient and outpatient registries for patients at Kyushu University Hospital between 1982 and 1996, standardised incidence rates (SIRs) (ratio of observed-to-expected cancers) were calculated in 43 patients with SSc, 24 patients with polymyositis (PM) and 17 patients with dermatomyositis (DM). Risk factors predisposing to cancers were also investigated in the SSc patients. Compared with the Japanese general population, the SIR for developing cancer in SSc patients was 5.1 (95% confidence interval (CI), 1.7–10.8), while the SIRs for cancer in the PM and DM groups were 4.7 (95% CI, 1.5–10.3) and 61.2 (95% CI, 46.8–77.6), respectively. A statistically significant risk factor for cancers in the SSc patients was positivity for anticentromere antibody (ACA) ($p < 0.05$), while the erythrocyte sedimentation rate, serum lactate dehydrogenase concentration, serum γ-globulin concentration, titre of antinuclear antibody and positivity for antitopoisomerase I antibody were not associated with cancer in SSc. Our population-based study confirms the increased risk of cancer among patients with SSc in Japan and provides new evidence that positivity for ACA should be considered as a risk factor for cancer in future monitoring of patients.

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Keywords: Anticentromere antibody; Cancer; Systemic sclerosis

Introduction

Systemic sclerosis (SSc) is a connective tissue disease that often involves systemic organs, especially the skin, lungs and alimentary tract. Recent epidemiological studies have shown that patients with SSc are at increased risk of developing cancer, and standardised incidence rates (SIRs) (ratio of observed-to-expected cancers) for such patients have been calculated as 1.5–4.6 [1–4]. It remains unknown, however, what role SSc plays in the development of cancer. Although Abu-Shakra et al. [2] demonstrated that patients more than 50 years old at the time of diagnosis of SSc were at significant risk for cancer, on the whole there have been few reports on significant risk factors for cancer in SSc patients. In Japan as well, there is increasing evidence of an association between SSc and cancer [4,5], including the results of a statistically estimated population-based study of cancer risk among Japanese SSc patients [4]. However, there have been no reports comparing the risk of cancer in patients with SSc with the risks in polymyositis (PM) or dermatomyositis (DM), which are considered to be more commonly associated with cancer. Also, there have been no reports about risk factors for cancer in Japanese SSc patients.

In the present study, we analysed SIRs for cancer and its risk factors in 43 Japanese patients with SSc. For the purpose of comparison, SIRs in 24 patients with PM and 17 patients with DM were also studied.

Patients and Methods

Patients

The diagnosis of SSc was made based on the diagnostic criteria for SSc proposed by the American Rheumatism Association (ARA) [6]. SSc patients in this study ($n = 43$) did not include any of the CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia) variants. PM patients ($n = 24$) and DM patients ($n = 17$) fulfilled the diagnostic criteria of Bohan and Peter [7]. All patients in our study were Japanese and had been treated as outpatients or inpatients at Kyushu University Hospital between 1982 and 1996.

Anti-centromere antibody (ACA) and antitopoisomerase I antibody were measured by SRL Inc., using the oucterony and fluorescence antibody methods, respectively.

Statistical Analysis

The population of patients at risk was obtained by the person-years method. The observed numbers of incidences of cancer were compared with the expected numbers of incidences of cancer, which were calculated by multiplying the patients' calendar-, sex- and age-specific person-years at risk by sex- and age-specific incident rates from the Research Group for Population-Based Cancer Registration in Japan [8–10]. Multiplication of person-years under observation by the incidence rates yields the number of cancers that would be expected if patients with SSc experienced the same risk as that prevailing in the general population of Japan. Cancer risk was determined using the SIR, defined as the ratio of the observed to the expected number of cancers. The 95% confidence intervals (95% CI) for the SIR were calculated based on the assumption that the observed number of cancer cases in a specific category follows a Poisson distribution. A lower limit of the 95% CI that exceeded 1.0 was taken to indicate statistical significance.

Fisher's exact probability test was used for calculating potential associations between cancer incidence in SSc patients and their clinical manifestations considered as risk factors.

Results

We identified 43 patients with SSc (31 women, 12 men), 24 patients with PM (15 women, nine men), and 17 patients with DM (seven women, 10 men) during the study period. The maximum length of follow-up was 26 years, and the average duration of follow-up was 6 years. The person-years of SSc, PM and DM were calculated as 383, 245 and 97, respectively. Table 1 shows the site or type of cancer for each group. We observed seven cases of cancer among the 43 SSc, one case among the 24 PM and eight cases among the 17 DM patients. The risk for cancer was not significantly increased in any particular site or between the sexes. Table 2 shows the observed and expected cases of cancers by original diseases. The overall cancer SIRs for the SSc, PM and DM patients were 5.1 (95% CI, 1.7–10.8), 4.7 (95% CI, 1.5–10.3) and 61.2 (95% CI, 46.8–77.6), respectively, indicating significantly increased rates of cancer among patients with SSc or DM compared with those of the general Japanese population.

There were only three patients with the CREST syndrome who had been treated at Kyushu University Hospital in this study period. Two of them were positive for ACA, and one of these two ACA-positive patients had suffered from uterus cancer. These patients with the

Table 1. Number of subjects and observed cases of cancer

Original disease	Number of patients (male:female)	Observed cases of cancer (male:female)	Site or type of cancer							
			Stomach	Lung	Colon	Uterus	Ovary	Breast	Liver	Thymus
SSc	43 (12:31)	7 (3:4)	2	2	1	1			1	
PM	24 (9:15)	1 (1:0)							1	
DM	17 (10:7)	8 (3:5)	2	1	1	1	1	1		1

SSc, systemic scerlosis; PM, polymyositis; DM, dermatomyositis.

Table 2. Risk estimates for cancer (SIR) compared with the Japanese population

Original disease	Observed cases of cancer	Expected cases of cancer	SIR	95% CI	*p* value
SSc	7	1.4	5.1	1.7–10.8	<0.01
PM	1	0.2	4.7	1.5–10.3	<0.05
DM	8	0.1	61.2	46.8–77.6	<0.001

SSc, systemic scerlosis; PM, polymyositis; DM, dermatomyositis; SIR, standardised incidence rate; CI, confidence interval.

CREST syndrome had to be excluded from this study because the number of these patients was too small to analyse statistically.

The temporal relations between the diagnosis of cancer and the diagnoses of SSc and DM are shown in Fig. 1. Second cancers in SSc developed mostly after the diagnosis of SSc was confirmed, while most of the diagnoses of DM were made after the cancers had been detected. As shown in Fig. 1, there was a significant difference in the temporal relations of cancer diagnosis between SSc and DM.

To examine the risk for cancer in SSc patients, various risk factors were investigated, such as disease duration, extent of sclerosis, positive antitopoisomerase I antibody, positive ACA, erythrocyte sedimentation rate, serum lactate dehydrogenase concentration, serum γ-globulin concentration and titre of antinuclear antibody. As shown in Table 3, three of five ACA-positive SSc patients had cancer, while two of 26 ACA-negative SSc patients had cancer. ACA was a statistically significant risk factor for cancer in SSc patients (χ^2 = 8.482, $p < 0.05$). In contrast, there was no significant association between antitopoisomerase I antibody and cancer. There were no significant differences between SSc patients with and without cancer for the other clinical and laboratory parameters studied (data not shown).

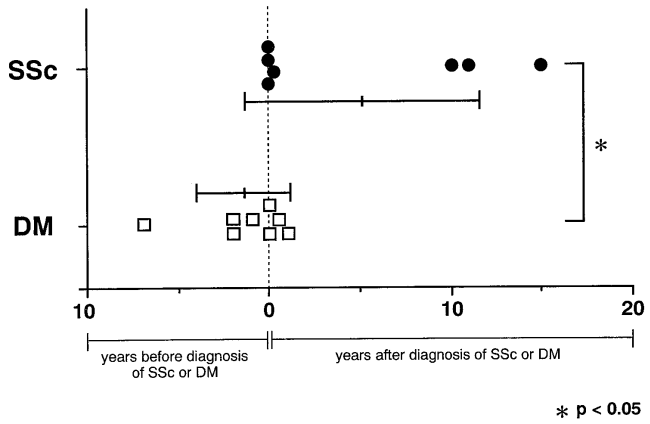

Fig. 1. Temporal relations between the diagnosis of cancer and the diagnosis of SSc or DM.

Table 3. Risk factors for cancer in patients with systemic sclerosis (SSc)

	SSc with cancer	SSc without cancer	
Antitopoisomerase I antibody			
Positive	3	15	] NS
Negative	2	16	
Anticentromere antibody			
Positive	3	2	] $p<0.05$
Negative	2	24	

Discussion

We found a significant increase in the risk for cancer in Japanese patients with SSc by population-based analysis. The incidence of concurrent or subsequent cancer in our 43 patients was 16.3%, with an estimated SIR of 5.1 ($p < 0.001$). This result is consistent with recent reports describing patients with SSc as being at higher risk for cancer, although earlier reports indicated no, or only a slight, association. Although in patients with SSc, lung cancer has been reported to be the most frequent malignancy [1–3, 5], our results did not demonstrate a significant association between SSc and any specific cancer site.

More importantly, we demonstrated here for the first time that positive ACA at the time of diagnosis of SSc is a significant risk factor for cancer. ACA has been suspected to be highly selective for CREST syndrome; however, in recent studies this antibody has been detected in 4–55% of patients with SSc [11–13]. Weiner et al. [14] reported an association between ACA and telangiectasia among scleroderma patients. Although patients with ACA were shown to have less severe diseases overall than those without ACA [15], Zuber et al. [11] demonstrated that four out of 45 patients positive for ACA were carrying malignant tumours, suggesting an association between ACA and malignant tumours. Although not statistically verified yet, an association between ACA and cancer among patients with SSc is also suggested.

Anti-topoisomerase I antibody, which is a specific autoantibody among patients with severe SSc, is also reported to be associated with cancer, and lung cancer in particular [16,17]. DNA-topoisomerase I is a nuclear enzyme that introduces and then repairs single- or double-stranded DNA breaks, and is overexpressed in many cancer types [18]. Kuwana et al. [16] have suggested that production of antitopoisomerase I antibody in SSc patients with cancer is due to an antigen-driven process. In contrast, our results did not show a significant association between antitopoisomerase I antibody and cancer in SSc. Further research, including larger aetiological studies, will be needed to explain this discrepancy.

There was a clear increase in the risk for cancer in patients with DM, a disease which has been strongly suggested to be associated with cancer [19]. Recent studies, including a controlled population-based analysis by Sigurgeirsson et al. [20], have confirmed the increased relative risk for cancer among DM patients and provided additional evidence to support the contention that this risk is most significant in patients with DM (SIR in males = 2.4, SIR in females = 3.4) as opposed to PM (SIR in males = 1.8, SIR in females = 1.7). In the present analysis comparing the cancer risk between SSc and DM, we demonstrated that this risk was also increased among patients with SSc, although the SIR among DM (61.2) was 12 times higher than that among SSc cases (5.1), which had a comparable SIR to that of the PM group (4.7).

There was a significant difference in the temporal relationships between the onset of SSc or DM and the diagnosis of cancer. Among eight patients with cancer and DM, three patients had histories of antecedent cancer, and the other five had cancer diagnosed within 1 year of the date of DM diagnosis. In contrast, none of the SSc patients were diagnosed as having cancers before the diagnosis of SSc, a finding that is compatible with previous reports [1–4]. Cancer among patients with DM can develop before, at the same time as, or after the diagnosis of DM [19]. Occasionally, cancer and DM seem to follow a parallel course, but more often the two conditions seem to be temporally related and to develop within 1 year of each other [19]. Based on the difference in the temporal relationships demonstrated in our report, cancers in patients with SSc might be considered to be developed by unknown mechanisms distinct from those of DM, such as immunosuppressive agents for the treatment of SSc or some autoimmunological abnormalities specific to SSc. The associations between cancer and other connective tissue diseases would seem to remain poorly understood [21], with the exception of an association between lymphoproliferation and Sjögren's syndrome [22].

It remains to be determined whether drugs used in treating SSc are in some way related to cancer development. Three of our SSc patients developed cancer more than 10 years after the diagnosis of SSc. They were given immunosuppressive agents for SSc treatment, such as D-penicillamine and cyclophosphamide. It is possible that these immunosuppressive agents may induce cancers in SSc as well as in rheumatoid arthritis [23,24]. There is no definite information in regard to this possibility, and further investigations will be needed.

In summary, this study demonstrates that the overall cancer risk is significantly increased in Japanese patients with SSc, as well as in those with DM. We also found that positive ACA is a risk factor for cancer in SSc patients. Lager studies will be needed to confirm these findings and to evaluate other risk factors among these patients.

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Received for publication 11 May 1999
Accepted in revised form 23 August 1999