Z Rheumatol 2022 · 81:522–523
https://doi.org/10.1007/s00393-022-01219-z
Accepted: 24 April 2022
Published online: 30 May 2022

Redaktion
U. Müller-Ladner, Bad Nauheim
U. Lange, Bad Nauheim

Cancer in systemic sclerosis: association between antibodies and malignancy

Cristiana Sieiro Santos[1] · Rúben Rego Salgueiro[2] · Clara Moriano Morales[1] · Carolina Álvarez Castro[1] · Elvira Díez Álvarez[1]

[1] Rheumatology Department, Complejo Asistencial Universitario de León, León, Spain

[2] Internal Medicine Department, Unidad Local de Saúde da Guarda, Guarda, Portugal

Dear Editor,

Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by fibrosis and vascular abnormalities in the skin, joints, and internal organs (especially the esophagus, lower gastrointestinal tract, lungs, heart, and kidneys). Systemic sclerosis is associated with an increased risk of malignancy. Risk factors predisposing an SSc patient to development of malignancy are not well defined, and the pathogenic basis of the association is yet to be explained. Some autoantibodies have been associated with a close temporal relationship to cancer. The absence of malignancy-screening guidelines tailored to SSc patients raises the importance of the need for more studies on the association between SSc and cancer.

In this retrospective cohort report, we determined the prevalence of cancer in SSc and studied the association between SSc-specific and SSc-associated autoantibodies in two centers with autoimmune diseases outpatient clinics. We conducted a retrospective cohort study by including patients diagnosed with SSc followed from 1980 to 2020 fulfilling the 2013 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) SSc criteria. Demographic features and clinical and immunological characteristics were retrieved. The primary outcome was SSc-associated cancer, defined as cancer occurring within 2, 5, and 10 years of first non-Raynaud SSc manifestation. The exposure was defined by the presence of SSc-specific/SSc-associated autoantibodies, including anti-centromere (ACA), anti-topoisomerase I (Scl70), anti-RNA polymerase III (anti-RNA pol III), anti-fibrillarin, anti-Th/To, anti-PM-Scl, anti-Ku, anti-TIF1g, and anti-Ro52. Descriptive analysis was used to compare clinical characteristics of subjects with cancer to those without cancer. Univariate logistic regression was used to compare the odds of SSc-associated cancer between the autoantibody subgroups.

Out of 123 SSc subjects, 35 (28%) had a history of cancer following their SSc diagnosis. Mean age was 65.9 (59–70) years, 67% were female, and 88% had a smoking history. Median time between cancer and disease onset was 5.33 (3.2–8.5) years. Among patients with cancer, 20 (57%) were diagnosed in the first 2 years after SSc onset, 8 (29%) were diagnosed after 2–5 years, and 7 (26%) were diagnosed 5–10 years after SSc onset. The most frequent malignancies were breast cancer ($n = 13$), lung cancer ($n = 6$), gastrointestinal cancer ($n = 5$), prostatic cancer ($n = 4$), hematological ($n = 3$) cancers, cervical/uterine cancers ($n = 2$), and non-melanoma skin cancer ($n = 2$). Patients with cancer were more likely to be Scl70 positive (odds ratio [OR] 2.55, 95% confidence interval [CI] 1.03–6.3, p 0.04), anti-TIF1g positive (OR 19.5, 95% CI 5.6–68.3, p 0.001), and anti-RNA pol III positive (OR 10.9, 95% CI 1.08–109.3, p 0.04); have a history of smoking (OR 7.24, 95% CI 2.6–197, p 0.001) and myositis (OR 5.2, 95% CI 2.06–13.2, p 0.005); and older age at SSc onset (61.9 vs. 57 years, p 0.04). Breast cancer was more frequent in anti-TIF1g (OR

Data availability
All data are available in the article.

Scan QR code & read article online

Table 1 Logistic regression analysis for the risk of cancer within 2, 5, and 10 years of SSc onset according to antibody positivity			
	OR 95% CI for cancer diagnosis within 2 years of SSc onset	**OR 95% CI for cancer diagnosis 2–5 years of SSc onset**	**OR 95% CI for cancer diagnosis 5–10 years of SSc onset**
Anti-Scl70	1.56 (0.51–44.5)	1.41 (0.27–12.7)	2.1 (0.55–13.4)
Anti-centromere	1.72 (0.62–52.1)	1.52 (0.32–32.1)	1.69 (0.14–21.3)
Anti-TIF1g	3.9 (0.35–43.4)	2.1 (1.45–9.94)	0.42 (0.04–5.32)
ARN Pol III	3.5 (1.2–51.4)	1.9 (0.72–62.1)	–
Anti-PM Scl75/100	–	–	0.87 (0.04–1.98)
Anti-Ro52	2.5 (0.66–66.8)	2.0 (0.45–50.2)	0.63 (0.05–7.74)
OR odds ratio, *CI* confidence interval, *SSc* systemic sclerosis			

3.75, 95% CI 1.8–17.5) and anti-RNA pol-III (OR 7.14 95% CI 1.56–90.8) subgroups. Results from logistic regression analysis for the risk of cancer within 2, 2–5, and 5–10 years of SSc onset are summarized in **Table 1**. The risk of SSc-associated cancer was significantly increased among anti-TIF1g-positive subjects at 5 years after SSc onset (OR 2.1, 95% CI 1.45–9.94, *p* 0.04) and among anti-RNA-pol III-positive subjects at 2 years after SSc onset (OR 3.5, 95% CI 1.2–51.4, *p* 0.02).

The incidence of malignancy in SSc varies between studies. It can coincide with the diagnosis or may be a consequence of treatment for it or another condition [1–3]. In addition, malignancy has been described with both diffuse and limited SSc [4]. Many reports state that more women than men have been reported, with a mean age of 58 years [5]. The average duration of follow-up from SSc onset to development of cancer is typically 5–9 years [6]. The development of lung cancer in patients with SSc with lung involvement is very frequent, with some studies reporting an odds ratio of 5.9 for lung cancer [7]. The second most frequently diagnosed entity is breast cancer, and there are reports of other common malignancies such as gastrointestinal and hematological cancer [8, 9]. Our data coincide with most of the literature, as the majority of patients with a cancer history were women, with 5.33 years between disease onset and cancer diagnosis. Breast cancer was also very frequent; however, lung and hematological cancers were detected in only 6 and 3 patients in our series, respectively. We recognize that this study has limitations due to it is retrospective nature, requiring revision of patients' clinical history, and missing data.

In conclusion, anti-Scl70, anti-TIF1g, and anti-RNA pol III were associated with an increased risk of cancer. Breast cancer was the most frequent type of cancer. Smoking, myositis, and an older age at SSc onset were more frequent in subjects with cancer. Autoantibodies should be taken into account in cancer screening. Larger studies are needed to define the risk of SSc-associated cancer in different autoantibody subgroups.

Corresponding address

Cristiana Sieiro Santos, MD
Rheumatology Department, Complejo Asistencial Universitario de León
C/Altos de Nava, S/N, 24071 León, Spain
cristysieirosantos@gmail.com

Author Contribution. CS, RS, CM, CA, and ED designed the study. CS and RS carried out statistical analyses. All authors contributed to interpretation of data. CS and RS drafted the manuscript. CM, CA, and ED critically revised the article.

Declarations

Conflict of interest. C. Sieiro Santos, R. Rego Salgueiro, C. Moriano Morales, C. Álvarez Castro, and E. Díez Álvarez declare that they have no competing interests.

This study involves human participants and was approved by CAULE's Ethical Committee. The current study involved revision of medical documents; therefore, participants and/or their family were asked for permission before using data.

References

1. Bergamasco A, Hartmann N, Wallace L, Verpillat P (2019) Epidemiology of systemic sclerosis and systemic sclerosis-associated interstitial lung disease. clin Epidemiol 11:257–273. https://doi.org/10.2147/CLEP.S191418
2. Barnes J, Mayes MD (2012) Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. Curr Opin Rheumatol 24(2):165–170
3. Shah AA, Rosen A (2011) Cancer and systemic sclerosis: novel insights into pathogenesis and clinical implications. Curr Opin Rheumatol 23(6):530–535
4. Moinzadeh P, Fonseca C, Hellmich M, Shah AA, Chighizola C, Denton CP, Ong VH (2014) Association of anti-RNA polymerase III autoantibodies and cancer in scleroderma. Arthritis Res Ther 16(1):R53
5. Hill CL, Nguyen AM, Roder D et al (2003) Risk of cancer in patients with scleroderma: a population-based cohort study. Ann Rheum Dis 62:728–731
6. Derk CT, Rasheed M, Artlett CM, Jiminez SA (2006) A cohort study of cancer incidence in systemic sclerosis. J Rheumatol 33:1113–1116
7. Rosenthal AK, McLaughlin JK, Gridley G et al (1995) Incidence of cancer among patients with systemic sclerosis. Cancer 76:910–914
8. Scope A, Sadetzki S, Sidi Y, Barzilai A et al (2006) Breast cancer and scleroderma. Skin Med 5:18–24
9. Katzka DA, Reynolds JC, Saul SH et al (1987) Barrett's metaplasia and adenocarcinoma of the esophagus in scleroderma. Am J Med 82:46–52