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Cardiac involvement in systemic sclerosis: identification of high-risk patient profiles in different patterns of clinical presentation

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Letter to the editor

Systemic sclerosis (SSc) is a chronic connective tissue disease characterized by widespread microvascular damage, dysregulation of fibroblasts with collagen overproduction and excessive fibrosis of the skin and internal organs, as well as complex immune system abnormalities.[1–3]

Patients are classified into the diffuse cutaneous form of SSc (dcSSc) when skin thickening extends to the trunk and the proximal part of the limbs, and into the limited cutaneous form (lcSSc) when skin induration is limited to face, hands and feet.[4]

The heart is the major organ involved in SSc, being a poor prognostic factor and the leading cause of mortality.[5,6] Cardiac involvement is reported in 15–20% of patients and when sensitive tools are used, it has been estimated to occur in up to 100% of SSc patients.[1,4]

The aim of the present study was to investigate cardiac involvement in different patterns of SSc in order to identify patients at high risk of cardiopulmonary impairment.

Methods

We retrospectively analyzed data from 241 consecutive SSc patients referred to our University-based Rheumatology Centre from January 1999 to January 2014 (F/M 205/36; mean age 50.8 ± 14.7 years; mean disease duration 10.9 ± 7.0). In all cases, the diagnosis of SSc was done by an expert rheumatologist on the basis of a wider panel of clinical, serological and capillaroscopic parameters; moreover, they satisfied the new ACR/EULAR classification criteria.[7] Patients were classified on the extent of skin sclerosis as limited cutaneous scleroderma (lcSSc) and diffuse cutaneous scleroderma (dcSSc).[4] All patients underwent baseline and periodically clinical evaluation, including demographic, serological and laboratory, pulmonary and cardiological evaluation.

The protocol was approved by Local Ethical Committee (pr # 10693 25/05/2016). All patients signed an informed consensus document.

Serum autoantibodies

The presence of serum autoantibodies was investigated by means of standard techniques: antinuclear (ANA), anticentromere (ACA) and antinucleolar antibodies by indirect immunofluorescence on Hep-2 cell lines; anti-extractable nuclear antigen antibodies, including anti-Scl70, anti-Sm, anti-RNP, anti-SSA/SSB; antiphospholipid antibodies; liver autoimmune profile; rheumatoid factor and antibodies to cyclic citrullinated peptide.

Cardiac assessment

Cardiac assessment was performed every 6 months and included clinical evaluation, ECG and Doppler echocardiography.[8–12] Cardiac risk stratification was performed according to Framingham Score.[7] The right heart catheterization, when indicated, was performed according to current methodologies.[12,13]

Statistical analysis

Statistical analysis was performed using SPSS (IBM software, New York, version 22.0). We performed a logistic regression analysis to investigate the possible correlation outcome and cardiopulmonary involvement.

Comparison of data between groups was performed by ANOVA. The *t*-test was used to compare data within groups. $P < 0.05$ was considered statistically significant.

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Table 1 Clinical features, antibodies panel and biomarkers

Parameter	lcSSc	dcSSc	*P*
Sex, F/M	180/29	25/7	
Age (years)	51.84 ± 14.55	43.78 ± 14.14	0.0039
Follow-up duration (months)	67.14 ± 41.86	65.25 ± 36.191	ns
Disease duration (years)	11 ± 7.12	10.56 ± 6.42	ns
Death (%)	32 (15.30)	6 (18.75)	ns
Raynaud (%)	208 (99.50)	31 (96.80)	ns
Digital ulcers (%)	104 (49.76)	25 (69.70)	0.02
Myositis	9 (4.30)	7 (18.75)	0.007
Arthitis	32 (15.30)	7 (18.75)	ns
SCl 70 antibodies	61 (29.00)	27 (75.00)	0.0025
ACA antibodies	88 (42.00)	3 (9.3)	0.0081
ANOA antibodies	35 (16.7)	5 (12.50)	ns
ESR	51 (24.4)	18 (50)	0.05
CRP	34 (16.2)	15 (40)	0.025
Uric acid	10 (4.78)	3 (6.25)	ns
Creatinine	13 (6.2)	7 (18.75)	0.04

ACA, anticentromere; ANOA, antinucleolar antibodies; CRP, C-reactive protein; dcSSc, diffuse cutaneous form of SSc; ESR, erythrocyte sedimentation rate; lcSSc, limited cutaneous form.

Results

Thirty-two patients had dcSSc (13.27%) whereas 209 patients had lcSSc (86.73%). We did not report differences in sex and duration of disease, whereas dcSSc patients were younger than lcSSc (43.78 + 14.14 years vs. 51.84 + 14.55 years; $P < 0.01$; Table 1). The follow-up duration was similar in the two groups of patients and lasted 65.25 months in dcSSc and 67.14 in lcSSc ($P =$ ns).

Autoimmune and biomarkers pattern

SCl 70 was positive in a greater number of patients with dcSSc compared with lcSSc ($P = 0.0025$); on the contrary a greater number of patients with lcSSc developed ACA antibodies ($P = 0.0081$).

Patients with dcSSc showed a higher inflammatory status with increased erythrocyte sedimentation rate and CPR value (Table 1).

Cardiac involvement

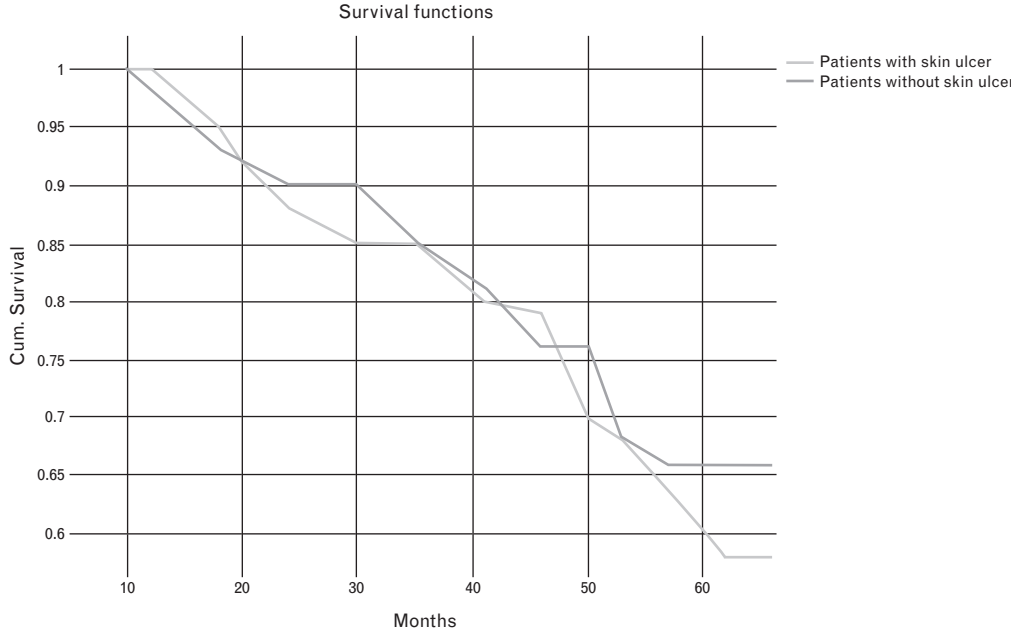
Cardiovascular involvement at baseline was present in 107 (51.2%) patients with lcSSc and in 13 patients (40.6%) with dcSSc. According to baseline data, we did not find differences between the limited and the diffuse presentation of SSc. However, the presence of skin ulcers was predictive of cardiac involvement [odds ratio (OR) 1.2; 95% CI 1.01–1.91; $P < 0.05$]. Then we categorized patients according to the presence of skin ulcers.[14] Skin ulcers were more frequent in dlSSc patients (7.9 vs. 18.1; $P = 0.05$).

Moreover, patients with ulcers showed a greater cardiac involvement. Specifically, they had more ECG alteration and ischemia (36 vs. 64%; $P < 0.05$). Left ventricular ejection fraction was also reduced in patients with ulcers (60 ± 4 vs. 58 ± 5; $P < 0.01$) and diastolic dysfunction showed deterioration during follow-up. Patients with skin ulcers had a greater cardiac mortality with a trend to significance (11.4 vs. 19.7%; $P = 0.08$; Fig. 1).

Comment

The present article evaluated the cardiac involvement in patients affected by SSc, in order to identify high-risk patients. Cardiac involvement is frequent in SSc and is

Fig. 1



Survival curves of patients with and without skin ulcers.

the most frequent cause of death.[4,15,16] The detection of cardiac manifestation in the early stage of the disease as well as their careful monitoring and follow-up are recommended to counteract their impact on the overall disease outcome. However, little information is available about the timing of cardiac involvement.[17]

We found that dcSSc patients had a greater inflammatory activation. A different immune pattern with a higher prevalence of SCl 70 antibodies in patients having dcSSc and a higher prevalence of ACA antibodies in patients with lcSSc was reported. Patients with ACA antibodies showed a greater cardiopulmonary involvement suggesting a worse prognosis. However, because of the low number of patients, we need more data to clarify the prognostic role of antibodies.[18,19]

The most significant parameter in prediction of outcome was the presence of skin ulcers.[14] We identify patients with skin ulcers as high-risk patients for cardiac disease. This confirms the analysis from the EUSTAR database.[20] These patients showed an increase in the number of arrhythmias during the follow-up; they mainly developed atrial fibrillation and supraventricular arrhythmias. Arrhythmias are associated with poor outcome and represent 6% of the overall causes of death in the large EULAR Scleroderma Trials and Research database.[21,22] In addition, our population of patients with skin ulcers showed a greater cardiac dysfunction involving both left and right sides of the heart and a greater deterioration of cardiac function over the follow-up.

In conclusion, cardiac involvement occurs frequently in SSc, can manifest in various ways and it is associated with a poor prognosis. There is little evidence on how best to detect and manage this fearful complication in SSc. According to our results, patients with skin ulcers are patients with high-risk profile of cardiovascular events and need a tight follow-up. A multidisciplinary cardiorheumatologic team is necessary to identify these high-risk patients.

Additional research by large population-based studies is needed in order to identify possible subsets of SSc patients at increased risk of cardiopulmonary complications.

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Conflicts of interest

There are no conflicts of interest.

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