Skin ulcers in systemic sclerosis: correlation with clinical phenotype in a monocentric cohort from the north-east of Italy


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Received on July 7, 2020; accepted in revised form on July 27, 2020.
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Key words: systemic sclerosis, digital ulcers, cohort study

ABSTRACT

Objective. To evaluate the prevalence of skin ulcers (SUs) and their association with clinical phenotype in a monocentric cohort of patients affected with systemic sclerosis (SSc).

Methods. Patients affected with SSc (ACR/EULAR 2013 criteria) in regular follow-up at the Rheumatology Unit of Padova University Hospital, Italy, were considered and retrospectively evaluated. Demographic, clinical and laboratory data, organ involvement and therapy were recorded. We analysed the occurrence, timing (single episode, recurrent/chronic) and site of SUs. The association between SUs and demographic and clinical variables was assessed by logistic regression analysis.

Results. We evaluated 211 SSc patients, aged 60.8±12.4 years, 187 (89%) females, 147 (70%) affected with limited cutaneous SSc. During a median follow-up of 120 months (50-216), 105 (50%) patients experienced at least one episode of SU; among them, 66% had recurrent or persistent SUs. Patients with a history of SUs compared with those never affected were younger at SSc diagnosis (p=0.009), had more frequently a diffuse cutaneous form (p=0.001), systemic inflammation (p=0.001), lung (p=0.002) and cardiac (p=0.004) involvement, and calcinosis (p=0.001). At multivariate analysis a younger age at SSc diagnosis (p=0.031), psoriasis (p=0.005) and telangiectasia (p=0.003) were independently associated with SUs. Telangiectasia, arthralgia involvement, chronic anaemia and inflammatory state were found to be associated with the recurrence/chronicisation of SUs.

Conclusion. SUs represent a common complication in our cohort of patients with a long-term follow-up. The association of SUs with some clinical manifestations of SSc suggests a combined role of microcirculatory damage and inflammation in their origin.

Introduction

Skin ulcers (SUs) are the most common clinical manifestations of vasculopathy in systemic sclerosis (SSc) (1, 2). Microangiopathic damage is responsible for several SSc manifestations such as Raynaud’s phenomenon (RP), telangiectasia, gastric antral vascular ectasia and life-threatening complications, e.g. scleroderma renal crisis (SRC) and pulmonary arterial hypertension (PAH) (3, 4). In this perspective the existence of a unified vascular phenotype of SSc has recently been hypothesised (5). Some studies revealed the association between peripheral vasculopathy detected by nailfold videocapillaroscopy and organ involvement, i.e. coronary microvascular dysfunction (6). Microvascular involvement plays a pivotal role in the pathogenesis of SUs (7), together with mechanical stress and inflammation, especially in SUs localised on bony prominence, joint contractures, or subcutaneous calcinosis (8). SSc-SUs are painful, often recurrent or persistent and require long time to healing (9). They lead to important limitations in the activities of daily living with a great impact on the quality of life of SSc patients (10-12). In this context, occupational therapy may have a role in order to improve their autonomy (13). About 20% of patients with SUs develop complications, such as infections, gangrene or amputation (14). In the European Scleroderma Trials and Research (EUSTAR) database 42.7% of SSc patients with diffuse cutaneous form (dcSSc) and 32.9% of those with limited cutaneous form (lcSSc) develop digital ulcers (DUs) (15). Notably, DUs are predictors of a worse disease course and mortality in scleroderma (16, 17).

Competing interests: none declared.
However, despite the high frequency and the prognostic value, there is no definitive consensus on how to exactly define DUs in SSc (18). Giuggioli et al. (19) has recently proposed a classification of SSc-SUs, based on the localisation of the lesions and the putative pathogenetic mechanism.

The aim of this study was to evaluate the prevalence of SUs and their association with clinical phenotype in SSc patients attending our referral centre for connective tissue diseases.

Patients and methods

Patients affected with SSc according to the ACR/EULAR 2013 criteria (20) attending the Rheumatology Unit of Padova University Hospital, Italy, from June 2017 to May 2018 were included in the study. We reviewed the medical charts of all patients with a follow-up visit at least every 6 months since the diagnosis of SSc (regular follow-up). Patients affected with SSc “sine scleroderma”, overlap syndrome or follow-up shorter than 24 months were excluded from the study. Patients were classified as having dcSSc or lcSSc according to LeRoy et al. (21) and disease duration was considered since the first non-Raynaud sign/symptom. Demographic, clinical and laboratory data were collected.

SU was defined as loss of substance involving epidermis and tissue under the basement membrane, until the bone in more severe cases. In accordance with Suliman et al. (22) abrasions and fissures, digital pitting scars and subungual hyperkeratoses were not considered as SSc-SU.

We registered SU occurrence and categorised patients as follows: no SU, isolate episode of SU, recurrent or chronic SUs (defined as more than one SU episode or SU episode lasting more than 6 months). Moreover, SUs were defined according to their localisation as DUs if they were on the fingertips or on toe tips, and SUs on the lower limbs if localised between the knees and ankle-feet (19).

As previously reported (23), organ involvements were defined as follows:
- pulmonary: evidence of interstitial lung disease (ILD) at high resolution computed tomography and/or restrictive lung disease on pulmonary function tests;
- cardiac: at least one condition among severe arrhythmias, cardiac conduction blocks, systolic (FE<55%) or diastolic dysfunction (according to the ASE criteria (24)), pericardial effusion (>10mm and diffuse);
- PAH: mean pulmonary arterial pressure ≥25 mmHg as assessed by right heart catheterisation with an estimated pressure in the left atrium (i.e. wedge pressure) ≤15 mmHg;
- gastro-intestinal: dysphagia and/or oesophageal radiographic dysmotility, symptoms of gastro-esophageal reflux, constipation, pseudo-obstruction, diarrhoea;
- renal: SRC and/or progressive renal failure.

Joint involvement was defined as the presence of inflammatory polyarthritis, arthritis and/or tendon friction rubs (requiring non-steroidal anti-inflammatory drugs and/or steroid therapy).

Chronic inflammatory syndrome and anaemia were considered as present if erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) were found >20mm/h and >6 mg/L, respectively, and haemoglobin (Hb) <12.5 g/dl in more than 5 determinations.

Exposure to pharmacological treatment was defined as a drug intake for at least 6 months at the conventional dosage, according to indications regularly approved for that drug. According to our clinical practice in presence of SUs at the lower limbs macrovascular involvement was investigated by Doppler ultrasound (US) and angiography when indicated.

Furthermore, smoking habit and traditional cardiovascular risk factors (i.e. diabetes mellitus, arterial hypertension, dyslipidaemia) were collected in all patients.

The study was approved by the institutional ethics committee and all patients gave written informed consent.

Statistical analysis

Categorical variables were reported as frequency and percentages, while continuous data as median and interquartile range or mean ± standard deviation (SD), as appropriate. Normality was tested with the Shapiro-Wilk test.

The patients were split into two groups: patients with versus patients without history of SUs. Patients with SUs were included into a subgroup analysis that compared patients who experienced a single episode of SU with those with recurrent/chronic SUs.

Categorical variables were compared using chi-square test or the Fisher exact test, while Mann-Whitney test or t-test for independent samples were applied for continuous variables.

Logistic regression univariate and multivariable analysis were performed to assess the independent association between SUs and demographic-clinical factors, including organ involvement. The covariates for multivariable models were chosen based on literature data or a p-value <0.2 at the univariate analysis results (only variables with a p-value less than 0.2 were included) and adjusted for age and sex. To avoid colinearity, only variables with variance inflation factor (VIF) <2 were retained in the multivariable models.

Univariate and multivariable analysis to assess the independent association between recurrent/chronic ulcers and the other variables were not carried out due to the relatively low number of events and the high risk of overfitting. The level of significance considered was alpha ≤0.05. All statistical analyses were carried out using IBM SPSS Statistics for Windows, v. 24.0, IBM Corp., Armonk, NY, USA.

Results

Two hundred and eleven patients were included in the study: 187 females and 24 males, aged 60.8±12.4 years, 147 (70%) with lcSSc and 64 (30%) with dcSSc. During the median follow-up period of 120 months (50-216), 105 (50%) patients experienced at least one episode of SU: 74 only DUs, 11 only SUs in the lower limbs and 20 patients DUs plus lower limbs SUs. Demographic and clinical features observed in the whole cohort and according to the presence/absence of SUs are reported in Table I.

Patients with a history of SUs compared with those never affected with this com-
plication were younger at the onset of RP (p=0.003) and at SSc diagnosis (p=0.009). SUs were significantly more frequent in patients with dcSSc than in those with lcSSc (p=0.001).

Regarding clinical features ever, patients with SUs had more frequently lung involvement (p=0.002), cardiomegaly (p=0.004) and articular involvement (p=0.001), telangiectasia (p=0.001), pitting scars (p<0.001) and calcinosis (p=0.001) and elevated ESR (p=0.001). The frequency of PAH, gastrointestinal and renal involvement was similar in the two groups. Puffy hands were more commonly found in patients never affected by SUs (43% vs. 27%, p=0.027). Smoking habit and arterial hypertension tended to be more frequent in patients with SUs than in those without (p=0.074 and p=0.055, respectively).

At multivariate analysis the occurrence of SUs was independently associated with a younger age at SSc diagnosis (OR 0.97, IC 0.94–0.99, p=0.031), articular involvement (OR 2.7, IC 1.4–5.3, p=0.005), and telangiectasia (OR 2.7, IC 1.4–5.2, p=0.003) (Table II).

No difference was found in the sub-analysis considering the classical cardiovascular risk factors in patients with SUs of the lower limbs versus patients with DUs only.

Among the 105 patients who experienced at least one episode of SUs, 36 (34%) had an isolate episode, whereas 69 (66%) had recurrent episodes or persistent SUs (Table III). In 70/105 cases (67%), SUs occurred during the first 3 years of the disease. The recurrence of SUs was associated with longer disease duration [168 (96-219) vs. 105 (33-180) months, p=0.04]. No significant association with sex and cutaneous form was observed. Anaemia (p=0.005), increased ESR (p=0.008) and CRP (p=0.004) were more frequently observed in patients with recurrent/chronic SUs compared to those with a single episode. The former also had more frequently articular involvement (p=0.028), pitting scars (p=0.044) and telangiectasia (p=0.001), as shown in Table III.

Patients who experienced recurrent/persistent SUs in comparison to those with a single episode required low-dose aspirin more frequently (75% vs. 40%), IV prostanoids (85% vs. 42%) and/or endothelin receptor antagonists (58% vs. 17%) (p<0.001 in all cases) and opioids (27% vs. 0%, p=0.001). By contrast, the percentage of patients treated with calcium-channel blockers (90% vs. 86%, p=0.550) was similar in the two groups. Concerning patients with SUs in the lower limbs (31/105, 30%), 17/31 (54.8%) had macrovascular involvement, 14/31 (45%) had chronic ulcers, 6/31 (19%) received autologous skin grafting and 9/31 (29%) required amputation.
Discussion

About half of SSc patients experience at least one episode of SU during the disease course, making this complication one of the most frequent in SSc. In line with previous reports (15, 17, 25, 26), we found that SUs were associated with younger age at SSc onset and occurred early in the disease course (i.e. within 3 years in about two-thirds of our cases). Moreover, opioids were often required for pain management in our cohort. These findings highlight the importance of a timely and effective treatment with vasodilators and might explain the great impact of SUs on SSc patients’ quality of life and work ability. Hence the importance of characterising SSc patients who experience SUs. One or more episodes of SU occurred in half of our patients during a long-term

Table II. Variables associated with SUs ever at univariate and multivariate logistic regression analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th></th>
<th>Multivariate analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p</td>
<td>OR (IC95%)</td>
<td>p</td>
<td>OR (IC95%)</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.08</td>
<td>2.2 (0.9-5.4)</td>
<td>0.28</td>
<td>1.8 (0.6-5.8)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>0.01</td>
<td>0.98 (0.95-0.99)</td>
<td>0.031</td>
<td>0.97 (0.94-0.99)</td>
</tr>
<tr>
<td>Diagnostic latency</td>
<td>0.65</td>
<td>1.0 (0.9-1.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-Scl70</td>
<td>0.026</td>
<td>1.9 (1.1-3.4)</td>
<td>0.09</td>
<td>1.1 (0.5-2.5)</td>
</tr>
<tr>
<td>dcSSc</td>
<td>0.001</td>
<td>2.8 (1.5-5.2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lung involvement</td>
<td>0.003</td>
<td>2.5 (1.4-4.5)</td>
<td>0.4</td>
<td>1.4 (0.6-2.9)</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>0.005</td>
<td>3.2 (1.4-7.4)</td>
<td>0.065</td>
<td>2.6 (0.9-7.1)</td>
</tr>
<tr>
<td>Gastro-intestinal involvement</td>
<td>0.8</td>
<td>1.1 (0.6-2.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>0.45</td>
<td>1.7 (0.4-7.5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Articular involvement</td>
<td>0.001</td>
<td>2.5 (1.4-4.5)</td>
<td>0.005</td>
<td>2.7 (1.4-5.3)</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>&lt;0.001</td>
<td>3.0 (1.7-5.5)</td>
<td>0.003</td>
<td>2.7 (1.4-5.2)</td>
</tr>
<tr>
<td>Calcinosis</td>
<td>0.001</td>
<td>4.3 (1.8-10.2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pitting scars</td>
<td>&lt;0.001</td>
<td>19 (9-41)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>0.058</td>
<td>2.0 (1.0-4.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Smoke ever</td>
<td>0.089</td>
<td>3.2 (0.8-12.1)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CI: confidence interval; dcSSc: diffuse cutaneous systemic sclerosis; Scl70: anti-topoisomerase I; SUs: skin ulcers.

Table III. Demographic and clinical features in patients with a single episode vs. recurrent/persistent SUs ever.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Single episode (36)</th>
<th>Recurrent/persistent episodes (69)</th>
<th>p-value</th>
<th>OR (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>31 (86)</td>
<td>58 (84)</td>
<td>0.758</td>
<td></td>
</tr>
<tr>
<td>Age at Raynaud’s phenomenon, mean (SD) years</td>
<td>40.6 (12.3)</td>
<td>39.3 (15.2)</td>
<td>0.661</td>
<td></td>
</tr>
<tr>
<td>Age at SSc diagnosis, mean (SD) years</td>
<td>44.2 (10.9)</td>
<td>46.3 (14.7)</td>
<td>0.425</td>
<td></td>
</tr>
<tr>
<td>Diagnostic latency, mean (Q1-Q3), years</td>
<td>1 (0-2.3)</td>
<td>1.5 (0-4.3)</td>
<td>0.754</td>
<td></td>
</tr>
<tr>
<td>Disease duration, mean (Q1-Q3), months</td>
<td>105 (33-180)</td>
<td>168 (96-219)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>dcSSc, n (%)</td>
<td>14 (39)</td>
<td>29 (42)</td>
<td>0.711</td>
<td></td>
</tr>
<tr>
<td>Autoantibodies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA, n (%)</td>
<td>13 (37)</td>
<td>27 (39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Scl70, n (%)</td>
<td>14 (40)</td>
<td>33 (48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-RNApolIII, n (%)</td>
<td>2 (6)</td>
<td>2 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia (Hb &lt;12.5 g/dl), n (%)</td>
<td>6 (17)</td>
<td>7 (10)</td>
<td>0.639</td>
<td></td>
</tr>
<tr>
<td>Anaemia without specificity, n (%)</td>
<td>5 (15)</td>
<td>27 (44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP &gt;6 mg/L, n (%)</td>
<td>2 (6)</td>
<td>21 (32)</td>
<td>0.005*</td>
<td>4.3 (1.5-12.7)</td>
</tr>
<tr>
<td>ESR &gt;20 mm/h, n (%)</td>
<td>4 (12)</td>
<td>25 (38)</td>
<td>0.004*</td>
<td>7.2 (1.6-33.1)</td>
</tr>
<tr>
<td>Lung involvement, n (%)</td>
<td>12 (35)</td>
<td>33 (49)</td>
<td>0.182*</td>
<td></td>
</tr>
<tr>
<td>Heart involvement, n (%)</td>
<td>6 (17)</td>
<td>17 (26)</td>
<td>0.294*</td>
<td></td>
</tr>
<tr>
<td>PAH, n (%)</td>
<td>1 (3)</td>
<td>4 (6)</td>
<td>0.659*</td>
<td></td>
</tr>
<tr>
<td>G-I involvement, n (%)</td>
<td>28 (80)</td>
<td>52 (79)</td>
<td>0.586</td>
<td></td>
</tr>
<tr>
<td>Renal involvement, n (%)</td>
<td>1 (3)</td>
<td>4 (6)</td>
<td>0.659*</td>
<td></td>
</tr>
<tr>
<td>Articular involvement, n (%)</td>
<td>13 (36)</td>
<td>40 (59)</td>
<td>0.028*</td>
<td>2.5 (1.1-5.8)</td>
</tr>
<tr>
<td>Telangiectasia, n (%)</td>
<td>14 (44)</td>
<td>49 (79)</td>
<td>0.001*</td>
<td>4.8 (1.9-12.3)</td>
</tr>
<tr>
<td>Puffy fingers, n (%)</td>
<td>15 (44)</td>
<td>12 (19)</td>
<td>0.009*</td>
<td>0.3 (0.1-0.8)</td>
</tr>
<tr>
<td>Pitting scars, n (%)</td>
<td>20 (59)</td>
<td>50 (78)</td>
<td>0.044*</td>
<td>2.5 (1.1-6.1)</td>
</tr>
<tr>
<td>Calcinosis, n (%)</td>
<td>6 (21)</td>
<td>23 (43)</td>
<td>0.057*</td>
<td></td>
</tr>
<tr>
<td>Smoke ever, n (%)</td>
<td>3 (8)</td>
<td>6 (9)</td>
<td>0.915</td>
<td></td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>7 (19)</td>
<td>17 (2)</td>
<td>0.497</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>0 (0)</td>
<td>3 (4)</td>
<td>0.198</td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>4 (11)</td>
<td>21 (31)</td>
<td>0.022*</td>
<td>3.7 (1.1-11.7)</td>
</tr>
</tbody>
</table>

OR: odds ratio; CI: confidence interval, SD: standard deviation; Q1-Q3: I quartile-III quartile; ACA: antcentromere; anti-Scl70: anti-topoisomerase I, anti-RNApolIII: RNA polymerase III; ANA: antinuclear antibodies; Hb: haemoglobin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PAH: pulmonary arterial hypertension; G-I: gastro-intestinal.; t-test; χ² test; Fisher test; Mann Whitney test.
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follow-up, more frequently in those with deSSc than in lcSSc, as reported in the EUSTAR cohort (27). However, the rate of recurrent/chronic SUs was similar between deSSc and lcSSc.

Regarding the autoantibody profile, the univariate analysis showed an association between SUs and anti-Scl70, as previously reported in some studies and in the Digital Ulcers Outcome (DUO) registry (16, 26, 28-30). Although SSc male patients often present a more severe disease, we did not find any association with male gender, in line with reports by the Canadian registry (26).

Our findings confirm previous reports showing a higher frequency of SUs in patients with cardiac involvement and ILD (26, 31); indeed, microangiopathy is thought to be one of the main pathogenic mechanisms either in SSc-SUs (mainly DUs) and in major organ involvement in SSc (5). We also found that SUs were associated with calcinosis and telangectasia, which seem also to be linked to the microvascular impairment in SSc patients (32, 33).

Nevertheless, there are conflicting studies on the association between PAH and SUs. Endothelial dysfunction is the main pathogenic mechanism in PAH and SUs – especially DUs – and the same categories of drugs (e.g. endothelin-1 antagonists) have been proposed in the management of these conditions. However, PAH does not seem to be associated with SUs in our cohort, but the small number of patients with PAH does not allow a definitive conclusion. Notably, we were able to demonstrate for the first time a significant association between SUs and joint involvement, chronic inflammation, and anaemia. It should be noted that all these clinical manifestations – unlike cardiac and pulmonary involvement, and calcinosis – were associated not only with the presence of SUs, but also with their recurrence/chronicity. Taken together, all these findings could have several explanations: first, the possibility of a more active/inflammatory disease in SSc patients with SUs, which is supported by the inclusion of DUs, inflammatory articular/periarticular manifestations (i.e. tendon friction rubs) and elevated CRP in the EUSTAR activity score, suggesting a role of inflammation in the pathogenesis of persistent/ recurrent SUs that, in turn, could explain the potential effectiveness of rituximab in some severe refractory cases of DUs (34). Second, chronic/recurrent SUs may trigger a chronic systemic inflammation state and concomitant infective complications in some cases.

Unlike ulcers of the upper extremity that have thoroughly been investigated and characterised in SSc, few studies on ulcers of the lower limbs are available to date. In our clinical practice, a Doppler US was performed in all patients with SUs of the lower limbs to assess macrovascular involvement, which we found in about half of our patients, slightly more than previously reported (35). This relatively high percentage suggests that microvascular dysfunction can be associated to macrocirculation impairment in patients with SSc-SUs of the lower limbs; thus, macrovascular assessment in these patients is recommended.

Ferri et al. (36) compared two large Italian SSC series, recruited before and after 2000, and found a decrease in the prevalence of SUs over time. This is in line with reports of a remarkably low number of new DUs in patients enrolled in recent RCTs, and might be due to a shorter disease duration at the first visit together with more effective vasodilator treatments, such as prostanooids and endothelin receptor antagonists (37-40). Moreover, the local management of SUs has substantially improved with topical treatment, regular medication and advanced dressings, following the TIME (necrotic Tissue, Infection/Inflammation, Moisture balance, and Epithelization) principles (41). One of the main strengths of our study is the homogeneous approach to diagnosis, classification and management of SUs, given its monocentric nature. A high number of patients followed up over a long period of time was included, making it one of the largest monocentric SSc-SUs studies in Europe. By contrast, the main limitation is due to its retrospective nature.

In conclusion, SUs emerged as a burdensome complication of SSc being recorded in about half of patients during a long-term follow-up, and often in a recurrent or chronic phenotype. SUs occur more frequently in deSSc and are associated with cardiac/pulmonary and articular involvement, and with increased ESR and CRP, suggesting a combined role of microcirculatory damage and inflammation in their pathogenesis.

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