Abstract

Objective. To evaluate in SSc, the frequency of digital lesions and the morphology, characteristics, natural course and time to healing of 1614 digital ulcers (DUs).

Methods. One hundred SSc patients were followed up for 4 years. In the first step, the digital lesions were observed and classified at the time of presentation [digital pitting scar (DPS); DU; calcinosis; gangrene]. In the second step, DUs were divided into subsets according to their origin and main features. In the third step, the time to healing was recorded for each DU and the influence of DU main characteristics on time to healing was also evaluated.

Results. In the first step, 1614 digital lesions were observed: DPS, 712 (44.1%) lesions; DU, 785 (48.6%); calcinosis, 110 (6.8%); and gangrene, 7 (0.8%). In the second step, DUs were subsetted as follows: DU developed on DPS (8.8%), pure DU; DU developed on calcinosis (60%); DU derived from gangrene. In the third step, the mean time to healing was 25.6 (15.6) days in DPS, 76.2 (64) days in pure DU, 93.6 (59.2) days in calcinosis ulcers and 281.1 (263.3) in gangrene.

Conclusions. In SSc, digital lesions are represented by DPS, DU, calcinosis and gangrene, and provide an evidence-based DU subsetting according to their origin and main characteristics. Subsetting may be helpful for a precise DU evaluation and staging, and in randomized controlled trials for a precise identification of those DUs that are to be included in therapeutic studies.

Key words: Systemic sclerosis, Digital ulcers, Calcinosis, Gangrene, Digital pitting scar.

Introduction

SSc is a multisystem disease characterized by significant dysfunction of the microvasculature, immune system and connective tissue. The microvascular involvement leads to clinical features that are the hallmarks of SSc, such as RP, digital ulcers (DUs), gangrene and autoamputation [1, 2].

In SSc, DUs are one of the most frequent complications at digital level, significantly reducing quality of life and requiring thorough work to achieve healing and to avoid infection, gangrene and autoamputation.

An Italian and a French study estimated the incidence of DU in SSc at 48 and 43%, respectively [3, 4]. In a retrospective study on an English cohort, 17.4% of 1168 SSc patients had at least one episode of vascular complications and 12.1% of the cohort required hospital admission for the management of vascular complications [5]. In a Canadian study, recurrent DUs were reported in 31.8–71.4% of SSc patients with progression to gangrene and autoamputation in 14–29% of cases [6].
Digital lesions may be characterized by DU, digital pitting scar (DPS), calcinosis and gangrene.

In the last decade, several randomized clinical trials have studied the effects of different drugs on the prevention and healing of DU in SSc ([7–9]; Matucci-Cerinic et al., submitted). In these trials, DUs are differently defined or classified and, as outcome measures, healing and the number of new DUs were used. Clinical care and bedside decision making would be facilitated by the availability of accurate and feasible criteria for DU classification. At international level, the classification of pressure ulcers is usually followed [10], but this classification is not adequate to the type of digital lesions seen in SSc. The lack of a clear classification of DU has prompted us to evaluate the frequency of digital lesions and the DU morphology, characteristics, natural course and time to healing in a cohort of SSc patients, followed up for 4 years.

### Patient and methods

From January 2004 to January 2008, 100 SSc patients presenting at least one digital lesion were consecutively observed and followed up at the Division of Rheumatology of the University of Florence. All patients agreed by written informed consent to participate in the study. Patients were classified into limited and dcSSc [11] and throughout the period of 4 years the occurrence of any digital lesion was recorded, clinically observed and studied methodologically in three consecutive steps.

In the first step, the digital lesions were observed and classified at the time of presentation, by the same operator (F.G.), as follows:

(i) DPS: it is defined as small-sized hyperkeratosis ([12]; Fig. 1a–c)

(ii) DU: it is defined as a loss of epithelialization and tissues involving, in different degrees, the epidermis, the dermis, the subcutaneous tissue and sometimes also involving the bone (Fig. 2)

(iii) calcinosis: it is defined as deposits of calcium phosphate in soft tissues, visible to the naked eye (Fig. 3b and c) and/or confirmed by X-ray (Fig. 3a)

(iv) gangrene: it is defined as the death of tissues caused by a total lack of blood supply. Macroscopically, the affected part is dry, shrunken and dark black (Fig. 4).

In the second step, DUs were divided into subsets according to their origin and main features. The following characteristics were recorded for each DU:

- DU-related pain, scored on a numerical rating scale (NRS 0–10) and divided into four categories: no pain (0), mild (1–3), moderate (4–7) and severe (8–10). Patients were also requested to specify whether pain was spontaneous or provoked by direct pressure.

- Indeed, every DU, according to the definitions proposed for pressure ulcers [10] and modified by us, was staged as follows:
  
  (i) Superficial: partial thickness skin loss involving epidermis. The ulcer is superficial and presents clinically as an abrasion, blister or tiny crater.

  (ii) Intermediate: full thickness skin loss involving damage to, or necrosis of, subcutaneous tissue that may extend down to, but not through, underlying fascia. The ulcer presents clinically as a deep crater with or without undermining of adjacent tissue.

  (iii) Deep: full thickness skin loss with extensive destruction, or damage to muscle down over the fascia, supporting structures (e.g. tendon, joint capsule) and bone.

In the third step, the time to healing was recorded for each DU and the influence of DU main characteristics on time to healing was also evaluated. Patients were clinically assessed, as previously reported [13], for lung involvement that includes the assessment of interstitial lung disease and pulmonary hypertension. The assessment of heart involvement (HI) is classically subdivided into two types: primary HI (autonomic neuropathy, myocardial fibrosis, small intra-myocardial coronary artery involvement and pericardial involvement) and HI secondary to either lung or kidney involvement. Renal involvement (renal hypertension and scleroderma renal crisis) and gastrointestinal involvement (oesophageal, stomach and bowel dysmotility) were also assessed. Patients were also studied with hand X-ray to detect possible tissutal digital calcinosis. The presence of infection was investigated with DU swab and culture. Patients were treated, with our local treatment protocol, always by the same operators (L.A., F.B.) as previously reported [14].

### Statistical analyses

All DU data were collected on a specific database (DAS-DU Scleroderma Digital Ulcers Database). Chi-square, Fisher’s, Mann–Whitney, analysis of variance, Welch, Levene, Cramer’s V and Lambda statistical tests were performed with SPSS-15 software. Statistical significance was set at \( P < 0.05 \).

Welch’s t-test is an adaptation of Student’s t-test intended for use with two samples having possibly unequal variances. Levene’s test is an inferential statistic used to assess the equality of variance in different samples. Some common statistical procedures assume that variances of the populations from which different samples are drawn are equal. Levene’s test assesses this assumption. It tests the null hypothesis that the population variances are equal. Cramer’s V coefficient was useful for...
comparing multiple chi-square test statistics and is generalizable across contingency tables of varying sizes. It is not affected by sample size and is therefore very useful in situations where it is suspected that a statistically significant chi-square was the result of large sample size instead of any substantive relationship between the variables. It is interpreted as a measurement of the relative (strength) of an association between two variables. Lambda is a test statistic used in multivariate analysis of variance to test whether there are differences between the means of identified groups of subjects in a combination of dependent variables.

### Results

Clinical and laboratory features of SSc patients are shown in Table 1. In 100 SSc patients, 1614 digital lesions were observed in 4 years: 439 (27.2%) in dcSSc and 1175 (72.8%) in lcSSc and the mean number of digital lesions per patient was 15.7 (17.7) [14.4 (12.2) in dcSSc and 16.2 (19.6) in lcSSc; \( P < 0.0001 \)]. Patients’ mean age was 57.7 (15.1) years.

The distribution of digital lesions was very close in both hands (right hand: 55%; left hand: 45%) with no difference between dcSSc and lcSSc and were localized more frequently on the second (24.5%) and third (26.6%) finger (Fig. 5a). The distribution on the fingers showed that digital lesions were more frequently localized on the fingertip (52%), on the dorsal area of the fingers (30%), seldom on the nail area (13%) and very rarely on the palmar area of the fingers (Fig. 5b). In the first step of the study, 1614 observed digital lesions were: 785 (48.6%) DU, 712 (44.1%) DPS, 110 (6.8%) calcinosis and 7 (0.8%) gangrene.

In the second step, all DUs were observed, studied and divided into four subsets according to their origin and main features.

(i) DU derived from DPS: in 8.8% of DPS (Fig. 1a and b), a DU was hidden below the hyperkeratosis; these DUs were easily identified as they were all characterized by inflammation and oedema of perilessional skin (Fig. 1d), by mild or moderate spontaneous pain, always superficial and were most frequently localized on fingertips (50%) and dorsal aspect of fingers (40%) (Fig. 5d). Dimensions were too small to be measured. The bed of the lesions were characterized by granulation tissue (78%) and seldom by fibrin (12%). Necrosis, infection,
gangrene, autoamputation, bone and tendon exposure were never detected. The mean time to healing was 25.6 (15.6) days (min = 12, max = 62) (Table 2).

(ii) Pure DU: these were mostly localized on fingertips (55.1%), nail folds (10.8%) and dorsal area of the fingers (30.6%) (Fig. 5), in particular on the superior aspect of the proximal interphalangeal joint (25.9%), MCP (6.7%) or on the phalanxes (7%) [1 phalanx (2.3%), 2 phalanx (1.7%) and 3 phalanx (3%)]. On fingertips, the mean dimension of DU was 51 (25.4) mm$^2$, significantly smaller than those localized on the 2$^\text{nd}$ dorsal phalanx [67.8 (58.4) mm$^2$; $P < 0.0134$]. Very frequently, DU had irregular borders (80.3%), oedema (56.4%) and inflammation of perilesional skin (75%). The stage was usually intermediate (59.8%) or deep (39.9%). In the bed of the lesion, fibrin (75.8%) (Fig. 2c and d) and granulation tissue (56%) (Fig 2a) were most frequently found. The majority of DUs did not have exudate (80.8%), when present, either at a low (54.6%) or high (69.2%) level, or with pus (92.9%) it was always associated with infection (Cramer’s $V = 0.484$, $P < 0.001$; $\lambda = 0.261$, $P < 0.001$). In DU, wet (8.8%) or dry (4.2%) necrosis, eschar (3.7%), gangrene, bone and tendon exposure (1.7%) and autoamputation (0.5%) were sometimes found. Spontaneous pain, moderate to severe, was present and, in particular when severe, it was significantly associated with infection (Cramer’s $V = 0.489$, $P < 0.001$) and inflammation of perilesional skin (Cramer’s $V = 0.559$, $P < 0.001$). The mean time to healing was 76.2 (64) days (min = 7, max = 810) (Table 2).

(iii) DU derived from calcinosis: more than half (60%) of the calcinosis developed a DU on any site of the hand, but most frequently on fingertips (71.2%) and nail area (16.6%) (Fig. 5e). The mean dimension was 43.1 (20.6) mm$^2$ with always irregular borders (80.3%), oedema (56.4%) and inflammation of perilesional skin (75%). The stage was usually intermediate (59.8%) or deep (39.9%). In the bed of the lesion, fibrin (75.8%) (Fig. 2c and d) and granulation tissue (56%) (Fig 2a) were most frequently found. The presence of stone (42.4%) (Fig. 3d), calci mousse (33.3%) (Fig. 3c) or pus mousse (24.2%) exudate was frequently associated with perilesional oedema (84.8%) and severe spontaneous pain (83.3%) (Table 2). The stage was almost always deep (90.9%) and seldom intermediate (9%), probably due to the localization of calcinotic deposition (Fig. 4d). In calcinosis-DU, the infection rate (40.9%) was higher than in other subsets and associated
with the presence of pus exudate (Cramer’s $V = 0.685$, $P < 0.001$; $\lambda = 0.593$, $P < 0.001$). The mean time to healing was 93.6 (59.2) days (min = 30, max = 388).

(iv) DU derived from gangrene: localized on fingertip. Mean dimension was 78.1 (36.4) mm$^2$. DUs derived from gangrene were always deep and characterized by irregular borders, inflammation and oedema of perilesional skin. Bone and tendon exposure (42.8%), necrosis (28.5%) and eschar (14.2%) were found and may lead to amputation (14.2%). Spontaneous severe pain was always present (Fig. 4, fifth finger of the left hand). The mean time to healing was 281.1 (263.3) (min = 40, max = 810) (Table 2).

In the third step, the data show that DU characteristics may significantly influence time to healing. The presence of fibrin ($P < 0.001$), oedema of perilesional skin ($P < 0.001$), wet or dry necrosis ($P < 0.001$), eschar ($P < 0.001$), bone and tendon exposure ($P < 0.001$) and gangrene ($P = 0.001$) delayed significantly the time to healing. The presence of infection was associated with a time to healing significantly longer ($P < 0.001$) and it was also associated with a deep stage (Cramer’s $V = 0.425$, $P < 0.001$) that was linked with a longer time to healing ($P < 0.001$) in pure DU. In contrast, the presence of granulation tissue and re-epithelialization were associated with a shorter time to healing ($P < 0.001$; Table 2). It is also clear that the overlap of some characteristics significantly delays healing. A DU that presents both granulation tissue and fibrin heals more slowly than a DU with only granulation tissue [49.9 (31.4) vs 31 (23.6); $P < 0.0001$]. The presence of fibrin in a necrotic DU also delays healing compared with a necrotic DU only [129.6 (55.8) vs 78.2 (41); $P = 0.005$]. Finally, no correlation between disease duration and DU occurrence or DU subset was found.

**Difference between diffuse and limited SSc**

DUs were more frequent in dcSSc (60.9%) than in lcSSc (47%). DPS and calcinosis evolving into DU were more frequently observed in lcSSc than in dcSSc patients (DPS-DU 74.6% in lcSSc vs 25.4% in dcSSc; calcinosis-DU 10.4% in lcSSc vs 1.4% in dcSSc; $P < 0.001$). In DU, inflammation of perilesional skin was more frequent in lcSSc (78.8%) than in dcSSc (68.1%) ($P < 0.001$). Also perilesional oedema was more frequently found in lcSSc (60.8%) than in dcSSc (48.1%) ($P < 0.0006$).
Infection was more frequently observed in lcSSc (36.7%) than in dcSSc (22.5%) \((P < 0.0001)\), developed very frequently on calcinosis-DU in lcSSc (43.5%), while in dcSSc it was never found, probably due to the low number (4) of calcinosis-DUs observed in dcSSc. In lcSSc, DPS-DU was more frequently localized on finger-tips (54.4%) than in dcSSc (35.4%) \((P < 0.001)\). DUs on the dorsal aspect of the fingers were more frequently
found in lcSSc (68.7%) than in dSSc (34.4%) \( (P < 0.001; \) Fig. 5). Gangrene was more frequently observed in dcSSc (0.9%) than in lcSSc (0.25%).

**Discussion**

Our data clearly show that the most frequently observed digital lesions in SSc are represented by DPS and DU, while calcinosis and gangrene are less frequent. Our work has also addressed the specific problem of DU and has also provided, for the first time, a differentiation of DUs according to their origin.

In SSc, a clinical evidence-based classification of DU is still lacking and today the increase in studies on DU highlights the need for a clear-cut classification of DU. This has become a major necessity to make both studies and outcomes uniform, as in previous randomized controlled trials (RCTs) and open studies, different definitions have been proposed. In RAPIDS-1, DUs were defined as a loss of surface epithelialization without including fissures or cracks in the skin or areas of calcinosis [7]. Similarly, Nithyanova et al. [5] have defined DU as ‘areas of loss of surface epithelialization affecting the digital pulp or bony prominence, not including fissures or areas of calcium extrusions’, while in other works a clear-cut definition is not provided [4, 15], and in the work of Abou Raya et al. [16], it was identified as loss of skin epithelialization only. After these definitions, we chose to consider the loss of epithelialization and the involvement of the lower layer as the fundamental items for a most adherent definition of what is seen in practice in DU in SSc.

In SSc, DUs are a heavy burden for the patient and the health systems [17]. In the 4-year follow-up the number of DU was significantly high in our patients. However, it is difficult to compare this datum with those obtained in other studies as we measured precisely the occurrence of every single DU and not the number of episodes of DU

**Table 2** Main features of DU subsets

<table>
<thead>
<tr>
<th>Dimension, mean (S.D.), mm²</th>
<th>78.1 (25.4)</th>
<th>51 (25.4)</th>
<th>51 (25.4)</th>
<th>43.1 (20.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrin, %</td>
<td>75.8</td>
<td>56</td>
<td>8.4</td>
<td>75.8</td>
</tr>
<tr>
<td>Granulation tissue, %</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Necrosis, %</td>
<td>17</td>
<td>37</td>
<td>17</td>
<td>37</td>
</tr>
<tr>
<td>Necrosis of perilesional skin, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Gangrene, %</td>
<td>1.7</td>
<td>3.7</td>
<td>1.7</td>
<td>3.7</td>
</tr>
<tr>
<td>Eschar, %</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Oedema of perilesional skin, %</td>
<td>28.5</td>
<td>28.5</td>
<td>28.5</td>
<td>28.5</td>
</tr>
<tr>
<td>Inflammation of perilesional skin, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Bone and tendons exposure, %</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Autoamputation, %</td>
<td>14.2</td>
<td>14.2</td>
<td>14.2</td>
<td>14.2</td>
</tr>
<tr>
<td>Time to healing, mean (S.D.), days</td>
<td>76.2 (64)</td>
<td>76.2 (64)</td>
<td>76.2 (64)</td>
<td>76.2 (64)</td>
</tr>
<tr>
<td>Pain</td>
<td>Mild moderate</td>
<td>Moderate severe</td>
<td>Severe</td>
<td>Severe</td>
</tr>
</tbody>
</table>

**Fig. 5** Right hand: DU with granulation tissue and fibrin on the second and third fingers. DU with fibrin on the fourth finger. On the fifth finger an initial gangrene is clearly visible. Left hand: DPS on the pulp of the first finger. DU with fibrin on the third and fourth fingers and gangrene of the fifth finger with bone exposure.
[4]. When two SSc subsets are analysed, our data show that the number of DUs is higher in dcSSc, in agreement with Ostojic et al. [18] who report a higher percentage of DU in dcSSc (67.5%) than in lcSSc (46.2%). It is interesting to remark that Ostojic et al. [18] found a total number of DUs derived from the addition of DPS and DU, showing that they considered DPS as DU even if not clearly defined in the manuscript.

For the first time in SSc, our data provide a description of digital lesions observed on SSc hand in practice and moreover provide a subsetting of DU based upon clinical evidence. This stems from clinical observation of DU, either in dcSSc or lcSSc patients, and is simple and may be used to identify DU seen in SSc clinics. The follow-up has shown that DPS and calcinosis may generate, through disepithelization or calcium deposit, respectively, a DU. This evidence clearly demonstrates that DPs are not a mere ischaemic cicatritial event, as previously proposed [17]. In every subset, the DU characteristics were also observed. DUs were measured when the dimensions allowed a clear evaluation: this was possible in DU, gangrene and calcinosis subsets only but not in DPS. These results are in agreement with Toffolo et al. [19], who found the measurement of DU diameter and area a reliable tool for assessment, and it was also used in other works to document outcomes [20, 21]. In other studies, such as [16] and RAPIDS-1 [7], the measurement of the dimensions of a DU was attempted through a camera but did not provide a significant result because of the evident high objective variability of the measurement. DUs were localized on different parts of the hand, mainly on the fingertips and on the finger’s dorsal area: in dcSSc, DUs were mainly seen on the fingertips and less frequently on the dorsal aspect of the finger on the upper part of IP joints. Usually, DUs over the finger joints have been considered mechanical, mainly due to skin retraction and not dependent on ischaemia [4] as the dorsal microvascular perfusion seems maintained in SSc fingers, whereas profound microvascular alterations are concentrated on the fingertips [22]. The characteristics studied in the four DU subsets are of importance mainly in the everyday clinic as well as they may be useful also in RCTs as outcome measures (such as dimensions or stage) or as inclusion or exclusion criteria.

Our work shows also that all DUs are painful and clearly demonstrate that when pain is present it is a pivotal symptom not to be neglected in practice because it may herald a threatening complication such as infection. Therefore, the cause of pain must always be carefully investigated and understood according to the ulcer subset and characteristics. In DU, pain is spontaneous and especially when severe, is linked in the largest majority of cases to infection, whereas in DPS spontaneous pain always hides an underlying DU. In DU due to calcinosis, pain is an important symptom and it is spontaneous but does not relate usually to infection as in the DU subset. Therefore, the cause of pain must always be investigated and pain must also be adequately controlled to alleviate the patient’s sufferance and ameliorate quality of life. In the future, pain, which is clearly a useful symptom in practice, may become an additional outcome measure in RCTs as it may be easily measured with a NRS or visual analogue scale.

The present work also attempts for the first time to provide in SSc a DU subsetting, staging as well as DU characteristics based on precise, internationally accepted, definitions and items derived from pressure wound ulcers. In all DUs, three different stages were always easily identified during each visit allowing a rapid and precise evaluation of the amelioration or worsening of a DU. Moreover, our study demonstrates that the DU subset and characteristics may significantly influence time to healing. It is clear that calcinosis and gangrene significantly delay the time to healing increasing the burden of DU in SSc patients. Indeed, the overlap of some ulcer characteristics, such as fibrin and infection, may further delay time to healing. In a previous work, Alivernini et al. [23] found that infection is the major risk factor of poor or no healing of DU, especially in the presence of evident signs of vascular sufferance (avascular areas) and inflammation.

In conclusion, our data confirm that digital lesions in SSc are represented by DPS, DU, calcinosis and gangrene and provide also a subsetting, according to origin and main characteristics, and staging, of the DU. The DU differentiation may be helpful in practice for a precise evaluation of the DU subset, characteristics and staging, and in future for a precise identification of those DUs that may be included or excluded in RCTs [24]. For example, an ulcer resulting from calcinosis probably is not responsive to vasodilator treatment as a purely ischaemic ulcer would be.

Further validation of the DU sub-setting and staging in an independent larger cohort is mandatory and, in future, it would be helpful to compare different cohorts of patients treated with the same local procedures.

Rheumatology key messages

- In SSc, digital lesions are represented by DPS, DU, calcinosis and gangrene.
- For a correct therapeutic strategy it is mandatory to know the DU subset, staging and characteristics.
- DU classification is useful for identifying which DU can be included in trials.

Disclosure statement: M.M.-C. has a consultancy relationship with Actelion Pharmaceuticals relevant to DUs. All other authors have declared no conflicts of interest.

References


