Digital Ulcers in Systemic Sclerosis – Frequency, Subtype Distribution and Clinical Outcome

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Abstract: Digital ulcers (DUs) are frequent and recurrent complication in systemic sclerosis (SSc) and are the main cause of pain, impaired function of the hand and disability in SSc.

The current study is a retrospective analysis of 60 SSc patients (47 patients with limited cutaneous SSc, 8 patients with diffuse cutaneous SSc and 5 patients with overlap syndrome, mean age 54.5±14.2 years, 52 women and 8 men). The frequency and evolution of DUs as well as the applied therapeutic strategies were analyzed. During the follow-up for a period between 6 months and 6 years, DUs at the fingers were registered in 35% of patients (21/60), more often in patients with diffuse cutaneous SSc (75%, 6/8) as compared with patients with limited cutaneous SSc (29%, 14/47, p<0.05) and overlap syndrome (20%, 1/5). The most frequently observed DUs were ischemic lesions at the fingerpads (85.7%, 18/21) and ulcersations over bony prominences of the fingers (23%, 5/21), which may be found simultaneously. More rare types of DUs were necrotic lesions (14%, 3/21). Thirty-eight percent (8/21) of the patients with DUs showed signs of inflammation. In one patient (4.76%, 1/21) an osteomyelitis developed and an amputation of a finger’s distal phalanx was performed. DUs at the toes were significantly less frequent as compared with DUs at the fingers (10%, 6/60, p<0.05). The period of healing of the DUs is prolonged and in the studied group was 3.39±2.39 months. The treatment regimen in SSc patients with DUs included vasodilators, local antiseptic treatment, antiplatelet drug; antiinflammatory in cases with development of necrotic lesions, antibiotics in cases of infection or necrotic lesions, and other symptomatic therapies. In conclusion, DUs are a common complication in SSc and require complex therapeutic measures for achievement of a positive outcome.

Keywords: Digital ulcers, systemic sclerosis.

INTRODUCTION

Microvascular involvement in systemic sclerosis (SSc) manifests clinically with Raynaud’s phenomenon (RP), digital ulcers (DUs), and sometimes gangrene, which are among the most characteristic features of the disease. RP in SSc is severe due to profound endothelial injury and DUs are a frequent and recurrent complication, which is the main cause of pain, impaired function of the hands and disability in SSc. In part of the cases, DUs may be complicated by infection of soft tissue or underlying bone, may require hospitalization and may lead to amputation of digits or even the complete hand. Approximately half of SSc patients are affected by DUs, and in 75% of cases the ulcers occur within 5 years of the first observation of non-Raynaud symptoms [1]. An analysis of the European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) database revealed a high frequency of DUs among the documented 3656 patients with SSc (1349 of whom had diffuse cutaneous SSc, 2101 had limited cutaneous SSc and 206 had SSc that overlapped with another connective tissue disease). Overall, 42.7% of the patients with diffuse cutaneous SSc and about 33% of those with the limited cutaneous form of the disease suffered from DUs that healed slowly (3–15 months) [2]. The following types of DUs are recognized: i/ “pure” DUs, defined as a loss of epithelialization and tissue compartments involving to a different degree, the epidermis, the dermis, the subcutaneous tissue and sometimes also the bone; ii/ DUs derived from calcinosis, which were defined as deposits of calcium phosphate in soft tissues, visible at physical examination and/or confirmed by X-ray; iii/ digital gangrenes, which were defined as necrosis of tissues caused by a total lack of blood supply with the affected part being macroscopically dry and necrotic [3]; iv/ DUs located over bony prominences, such as the interphalangeal joints [4].

PATIENTS AND METHODS

The current study is a retrospective analysis of 60 SSc patients (47 patients with limited cutaneous SSc, 8 patients with diffuse cutaneous SSc and 5 patients with overlap syn-
syndrome, mean age 54.5±14.2 years, 52 women and 8 men), treated in the Department of Rheumatology and Clinical Immunology, Kerckhoff-Klinik, Bad Nauheim, Germany (n=40) and in the Department in Rheumatology, MHAT “Health”, Medical section “Pulmed”, Plovdiv, Bulgaria (n=20). The follow-up of the patients was between 6 months up to 6 years. In these patients, the frequency, evolution of DUs and the applied therapeutic strategy were analyzed.

The presence of DUs of the fingers and toes was documented and lesions were categorized as described above: i/ DUs of the fingerpads or at the acral phalanges of the toes (pure DUs); ii/ DUs over bony prominences, iii/ digital gangrenes; iv/ DUs over calcinosis.

The following treatment regimens of SSc patients with DUs were analyzed:

1. Administration of vasodilators such as dihydropyridine calcium channel blockers with high vasoactivity (e.g. felodipine, or amlodipine), phosphodiesterase inhibitors (e.g. pentoxifyllin), or intravenous prostaglandins;
2. Antiplatelet drugs;
3. Anticoagulation therapy with enoxaparin or nadroparin, in cases with development of necrotic lesions;
4. Oral or intravenous antibiotics, e.g. quinolones, clindamycin, or metronidazole, in cases of infection or necrotic lesions;
5. Analgetics such as metamizole, paracetamol, or opioids, e.g. tramadol;
6. Local antiseptic treatment;
7. Discontinuation of treatment with immunosuppressants;
8. Surgical treatment such as debridement or amputation.

RESULTS

Clinical Presentation

During the follow-up period, DUs were registered in 29% (14/47) of the patients with limited cutaneous SSc, in 75% (6/8) of the cases with diffuse cutaneous SSc and in 20% (1/5) from the patients with overlap syndrome (overall frequency 35%, 21/60).

The most commonly observed DUs were ischemic lesions at the fingerpads (85.7%, 18/21) (Fig. 1) and ulcerations over bony prominences of the hands (23%, 5/21), which occurred simultaneously in some cases. In 5 patients from the examined group (23%), the concomitant occurrence of more than one type of DUs was observed, e.g. ulcers over bony prominences and at the fingerpads. The more rare type of DUs, but with more severe course regarding pain, functional impairment and duration of healing, are digital gangrenes, which were found in 14% (3/21) of the cases (Fig. 2). In our group of patients, we did not have cases with DUs derived from calcinosis.

![Fig. (1). Pure digital ulcers at the fingerpad in a female patient with limited cutaneous systemic sclerosis (red arrow).](image1)

![Fig. (2). Digital gangrenes in a female patient with limited cutaneous systemic sclerosis.](image2)

DUs at the toes were found significantly less frequently than DUs at the fingers. They occurred in 10% of the patients (6/60) vs 35% (21/60) at the fingers p<0.05), specifically in 3 patients with limited cutaneous SSc (6.38%, 3/47), in one patient with diffuse cutaneous SSc (12.5%, 1/8) and in two patients with overlap syndrome (40%, 2/5). The observed subtypes of DUs at the toes were from the following groups: 3 cases with DUs at the acral phalanges of the toes, 3 cases of DUs over bony prominences and 1 case with digital gangrenes (Fig. 3).

Therapy

The administration of a vasodilator was an obligatory step in all patients with DUs. All SSc patients with DUs received calcium channel blockers, e.g. felodipine (n = 8), am-
Iodipine (n = 8) and nifedipine (n = 5), which were administered as monotherapy in 5 patients, whereas in 16 patients calcium channel blockers were used in combination with either intravenous pentoxifyllin (n = 7) or with intravenous prostaglandins in 10-day courses (iloprost, n = 9). Among the 16 patients with ischemic DUs of the fingertips (i.e., pure DUs), 6 received a combination therapy of felodipine and intravenous pentoxifyllin, 8 a combination of amiodipine and intravenous iloprost, one a combination of nifedipine and intravenous iloprost, and one amiodipine.

All patients with DUs received low-dose aspirin (80 - 100 mg per day), one patient was on therapy with clopidogrel. Patients with digital gangrene (n = 3) received a 1-month therapy with subcutaneous low molecular weight heparin followed by low-dose aspirin after documented improvement had been achieved.

Thirty-eight percents (8/21) of the patients with DUs showed signs of inflammation (local redness, edema, elevated erythrocyte sedimentation rate and C-reactive protein), which required antibiotic treatment. Antibiotics were administered in all patients with digital gangrene (n = 3) and also in patients with other forms of DUs (n = 5), who showed the above-mentioned clinical and laboratory signs of inflammation, which were not associated with other clinical findings. Analgeics on demand were used in order to relief pain and improve the quality of life of the patients. Two of the patients were referred to a surgeon for consultation. Debridement was performed in two cases and amputation of a finger's distal phalanx was indicated in a single patient (4.76%, 1/21) with osteomyelitis.

Local antiseptic treatment was applied in all patients with DUs. Of note, immunosuppressants were discontinued in all SSc patients with DUs for 1-month period after consideration the stability of the concomitant disease presentations.

Outcome

With the described therapeutic regimens healing of DUs was achieved in 95% of the cases (20/21) (Fig. 4 and 5). Amputation of the distal phalanx was indicated in a single patient with osteomyelitis, which had been developed at the time of the referral to rheumatologist, which suggests the necessity of prompt therapy initiation. The mean time of healing of the DUs in the studied group was 3.4 ± 2.4 months and ranged between 2 and 12 months.

DISCUSSION

Frequency of Digital Ulcers

The performed retrospective analysis showed a frequency of DUs in the investigated group of SSc patients of 35%. This frequency is lower than those reported by other authors,

Fig. (3). Digital gangrenes of the toes in the same patient presented in Fig. (2).

Fig. (4). Pure digital ulcer at the fingertip of the index finger in a female patient with diffuse cutaneous systemic sclerosis (left). The patient was treated with felodipine, pentoxifyllin and low-dose aspirin plus local antiseptic treatment. Complete healing of the digital ulcer is demonstrated after 2 months of treatment (right).
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Fig. (5). Pure digital ulcer of the fingerpad of the ring finger in a female patient with diffuse cutaneous systemic sclerosis (left). The patient was treated with felodipine, pentoxifyllin, low-dose aspirin and local antiseptic treatment. Complete healing of the digital ulcer is demonstrated after 3 months of treatment (right).

e.g. 43% [1] and 48% [5] in other patient populations. The frequency of DUs in the current study is similar to those reported by Bérezný et al. in a population of 189 SSc patients, who have found at least one DU in 31.7% of the cases (60/189). Twenty patients (33.3%) had one DU, 40 (66.7%) had ≥1 DUs, and 24 (40%) had ≥ 4 DUs at the time of evaluation. A total of 54 patients (90%) had ≥ 1 fingertip DU. Twelve patients (20%) had ≥1 DUs associated with calcinosis, 15 (25%) had mechanical DUs proximal to the fingertip, and 16 (26.6%) had ≥ 1 DUs resulting from more than one mechanism [6]. The lack of DUs in the context of calcinosis in the current study may be related to the smaller patient number.

Diffuse vs. Limited Cutaneous form of SSc

Of note, DUs were observed more frequently in patients with diffuse cutaneous SSc (75%) as compared with individuals with limited cutaneous SSc (29%; p<0.05). Similarly, Amanzi et al. have also found significantly higher frequency of DUs (60.9%) in cases with diffuse cutaneous SSc in a cohort of 100 SSc patients in comparison with those with limited form of the disease [3].

Fingers vs. Toes

DUs at the toes were observed in 10% of the patients, which is significantly less frequently as compared with fingers (35%, p<0.05). La Montagna et al. in 100 SSc patients have found higher frequency of trophic changes (commonly DUs and digital pitting scars) at the feet (31%). The percentage of patients with trophic changes of the hands was 52% [7]. These findings are similar to our previous study in 36 SSc patients with frequency of DUs at the toes – 8.3% (3/36) vs. 36% (13/36) at the fingers (p<0.05). We have previously suggested, that the lower frequency of DUs of the feet is associated with the less severe RP, less frequent microvascular abnormalities and with the lower skin score in the feet [8]. In addition, involvement of the feet in SSc frequently occurs later in the disease course, while RP of the hands is the most frequent presenting feature, which in a high proportion of patients precedes other clinical phenomena of the disease by years [7]. Thus, more advanced microvascular changes and respectively DUs, which represent vascular complication, may be probably observed at the toes in a higher proportion of patients during a longer period of follow-up.

Therapeutic Approach

Considering the various pathogenetic mechanisms for the development of DUs, the treatment of the patients was complex and included as an obligatory component a vasodilator. According to the current EULAR recommendations for management of RP and DUs in SSc, dihydropyridine calcium channel blockers, usually oral nifedipine, should be considered for first-line therapy [9]. Apart from their efficacy in reducing the severity and frequency of vasospastic attacks, calcium channel blockers lead to healing of DUs, although the number of the studies addressing their efficacy in DUs is limited [10, 11]. In our previous study, we reported successful recovery of DUs in four SSc patients treated with the highly vasoselective calcium channel blocker felodipine. Felodipine showed superior efficacy in a head-to-head comparison with nifedipine and diltiazem [11]. The selectivity of felodipine to blood vessel/heart is 100:1, which is 7 times higher than that of nifedipine, whose selectivity is 14:1, and 14 times higher than that of diltiazem (7:1) [12]. Of note, the majority of patients with DUs in the current study – 71% (15/21) did not receive calcium channel blocker before the appearance of DUs vs. 29% (6/21) who develop DUs while being on the supportive treatment with dihydropyridine calcium channel blockers, e.g. 4 patients on felodipine and 2 – on amlodipine. Due to the small number of the observed group, conclusions about their protective effect on DUs development could not be made.

In the current EULAR recommendations for management of RP and DUs in SSc, it is postulated, that
intravenous prostanoids (in particular iloprost) should be considered in the treatment of active DU in patients with SSC as their efficacy has been proven in randomized placebo-controlled clinical trials [9, 13, 14]. EULAR experts underline that bosentan has no proven efficacy in the treatment of active DU in SSC patients, but has demonstrated efficacy in two randomized placebo-controlled clinical trials to prevent DUs in diffuse SSC, in particular in the patients with multiple DUs. Thus, it is suggested, that bosentan should be considered in diffuse cutaneous SSC with multiple DUs, after failure of calcium channel blockers and usually, prostanoid therapy [9, 15, 16]. In the present study, bosentan has not been initiated in SSC patients specifically for DUs. Its preventing effect in SSC patients, who had received it for the concomitant pulmonary arterial hypertension has not been analyzed in our retrospective study due to the small number of cases. Thirty-three percent (20/60) of the patients are from the Bulgarian cohort, where bosentan has become available just recently and in the period of the study none of the included patients received bosentan. In the remaining 67% (40/60), 13% (8/60) received bosentan for the treatment of concomitant pulmonary arterial hypertension, 4 of them were with and 4 without DUs. Due to the small number of cases, comparison and conclusion could hardly be performed.

Medication for the prevention of thrombus formation was the next obligatory step in the therapeutic approach. All patients with DUs received low-dose aspirin (80 – 100 mg per day), one patient was on therapy with clopidogrel. Patients with digital gangrenes (n = 3) received a one-month therapy with subcutaneous low-molecular heparin followed by low-dose aspirin after documented improvement. The severe endothelial damage in SSC is supposed to lead to subsequent loss of the physiological function of the endothelium to prevent thrombus formation. Despite increasing evidence of disturbed platelet function and activation of the coagulation system in SSC in the context of profound endothelial damage as a primary trigger event, data addressing the therapeutic effect of antiplatelet agents and anticoagulants are limited. Thus, the administration of antiplatelet drugs and anticoagulants in DUs caused by SSC-related vasculopathy is based on the current knowledge on the underlying pathogenesis and on experts' opinion [17]. Local antiseptic treatment is an obligatory step in the treatment of DUs in SSC. Surgical procedures are performed when indicated. Temporary discontinuation of immunosuppressors should be considered if the concomitant disease presentations are stable.

Outcome

We have analyzed retrospectively the complex therapeutic approach in SSC patients with DUs including local antiseptic treatment, discontinuation of immunosuppressants, vasodilators (e.g. dihydropyridine calcium channel blockers, intravenous pentoxifyllin, intravenous iloprost), antiplatelet drugs, anticoagulants and surgical procedures when indicated. Prospective controlled trials addressing the therapeutic effect of antiplatelet drugs and anticoagulants in SSC patients with DUs are lacking, but the current knowledge about the profound vascular dysfunction, which triggers thrombosis, suggests a potential benefit from their administration. With this therapeutic approach, we have observed a positive outcome in the majority of the patients (95%, 20/21), (Fig. 6).

Amputation of a finger’s distal phalanx was indicated in a single patient with osteomyelitis, which had been developed at the time of the referral to rheumatologist, which suggests the necessity of prompt therapy initiation.

The time of healing with adequate treatment in our group was long (3.4 months; range 2-12 months) and is similar to that reported by other authors, e.g. 3-15 months [2].

Fig. (6). Suggested therapeutic regimen for patients with different subtypes of digital ulcers.
CONCLUSION

DUs are a frequent and recurrent complication in SSC and are the main cause for impaired function and disability in these patients. According to published data and the results of the current study, DUs are more frequent in patients with diffuse cutaneous SSC. Similarly, parallel to the less severe RP and the milder clinical involvement, the toes are affected less frequently by DUs than the fingers. The therapeutic approach in SSC patients with DUs is still a challenge for the rheumatologist and only a multifaceted approach leads to a positive outcome.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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