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Concise report

Digital ulcers as a sentinel sign for early internal organ involvement in very early systemic sclerosis

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Abstract

Objective. The aim of this study was to evaluate the presence of digital lesions in very early diagnosis of SSc (VEDOSS) patients and its possible association with internal organ involvement.

Methods. One hundred and ten VEDOSS patients were investigated for the presence of digital ulcers (DUs), digital pitting scars, calcinosis, necrosis or gangrene, nailfold videocapillaroscopic abnormalities, disease-specific autoantibodies (ACA and anti-topo I) and internal organ involvement.

Results. Four patients reported a history of digital pitting scars, while 25 patients presented an active DU or reported a history of DUs. In particular, 16 patients presented with active DUs (14/16 also reporting a history of previous DUs), while the other 9 patients reported a history of DUs only. A statistically significant association between DUs and oesophageal manometry alteration was found in the whole DU population, as well as in the history of DU and the presence of active DU with/without a history of DU subgroups ($P < 0.01$, $P = 0.01$ and $P < 0.05$, respectively). DUs were observed in VEDOSS patients with internal organ involvement but not in those without organ involvement.

Conclusion. DUs are already present in VEDOSS patients characterized by internal organ involvement, significantly correlating and associating with gastrointestinal involvement. DUs may be a sentinel sign for early organ involvement in VEDOSS patients.

Key words: very early systemic sclerosis, digital ulcers, oesophageal involvement.

CLINICAL SCIENCE

Introduction

SSc is a major challenge for the rheumatologist, as its diagnosis is difficult in the very early/early phase of the disease [1]. For this reason, great interest is devoted today to patients with very early diagnosis of SSc (VEDOSS), when the degree of vasculopathy and fibrosis still have a minimal clinical impact [2]. The diagnosis of very early SSc is highly suspected in the presence of the so called red flags: RP, puffy fingers and ANA. The suspicion is then confirmed by the positivity of either ACA or anti-topo I positivity and/or a nailfold videocapillaroscopy (NVC) scleroderma pattern [2].

Usually in established SSc, one of the main vascular complications is digital ulcers (DUs) [3], which are a significant burden to SSc patients [4]. Therefore the problem of DUs has been considered as a clinical priority and randomized clinical trials have been designed to prevent and heal DUs [5]. In SSc, DUs appear early [6], may significantly lower the patient's quality of life and may be a harbinger of a poorer prognosis [7, 8]. For this reason, the prompt identification and management of DUs is mandatory. The aim of the present study was to evaluate whether in VEDOSS patients digital lesions, and in particular DUs, could be detected early and whether their presence is associated with internal organ involvement [7].

Methods

In the VEDOSS Clinic of the Department of Clinical and Experimental Medicine, Section of Rheumatology, Azienda Ospedaliero Universitaria Careggi (AOUC) of the University of Florence, 316 RP patients were enrolled in

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the VEDOSS study from March 2010 to May 2012. These patients are part of a larger cohort of patients involved in the multicentre VEDOSS study [9]: 110 patients were classified as VEDOSS according to the presence of preliminary criteria (RP, puffy fingers, ANA, plus NVC abnormalities and/or disease-specific antibodies) [2]. Other causes of digital vasculopathy, such as diabetes, cryoglobulinaemia, arterial hypertension and haematological diseases, were ruled out and smoking history was reported by 17% of the population. NVC was performed by trained physicians (C.B., G.L.) and images were classified into scleroderma patterns (early, active or late) according to the methodology and previously proposed classification [10]. In every patient, demographic data [age, sex, disease duration (defined as the time since RP onset)] were recorded during the first visit. The following signs and symptoms were investigated: presence of active DUs or a history of DUs as previously defined by Amanzi *et al.* [4], oesophageal symptoms (heartburn and dysphagia), digital numbness (median nerve compression), dyspnoea, pitting scars, calcinosis and telangiectases and modified Rodnan skin score. All 110 patients were investigated for internal organ involvement, such as interstitial lung disease (ground glass, reticular or honeycombing pattern of pulmonary fibrosis), on chest high-resolution CT (HRCT), impairment of pulmonary function tests with/without a reduction in the diffusion capacity of carbon monoxide (DL_{CO}) and a dysfunctional oesophageal lower sphincter on oesophageal manometry (with basal low pressure <15 mmHg). Ethics approval was obtained from the Bioethical Committee of the AOUC of Florence, Italy. All participants provided written informed consent to participate in the study. Statistical analysis were performed using SPSS Statistics version 19 (IBM, Armonk, NY, USA) through chi-squared and Fisher's exact tests to test the association between binomial variables, while the Mann–Whitney *U* test was used to compare continuous variables.

Results

Clinical characteristics of the VEDOSS patients

ACA was positive in 59/110 patients, while anti-topo I positivity was found in 21/110 patients. NVC showed a scleroderma pattern in 80/110 patients (50/80 early and 30/80 active pattern). In the cohort of 110 VEDOSS patients, only 4 patients [3.6%; 4 female, mean age 52 years (S.D. 11)] reported a history of digital pitting scars; 25 patients [23%; 22 female and 3 male, mean age 51.5 years (S.D. 13.8), mean time from RP onset 9.2 years (S.D. 6.3)] presented a DU or reported a history of previous DUs. In particular, 16 patients [15%; 13 female and 3 male, mean age 47.4 (S.D. 9.5), mean time from RP onset 8.9 years (S.D. 6.2)] had active DUs at the moment of first presentation to our centre or during follow-up visits. The majority of these patients (14/16) also reported a history of previous DUs. Another nine patients [8%; 9 females, mean age 58.6 years (S.D. 17.7), mean time from RP onset 9.6 years (S.D. 6.9)] reported a history of DUs only. No patient showed or reported the presence of tissue necrosis, gangrene or calcinosis. Patient characteristics are shown in Table 1.

VEDOSS patients with DUs

In the group of 25 patients with DUs and/or a history of DUs, ACA/anti-topo I were detected in 17 patients, while an early NVC pattern was detected in 19 and an active NVC scleroderma pattern was seen in 5. These two NVC SSc patterns were more frequently seen in patients with a DU (96%) compared with those without a history nor present DUs (66%), showing a statistically significant association with presence/history of DU ($P < 0.01$), in particular regarding the early scleroderma pattern ($P < 0.01$). Telangiectases were also associated with DUs ($P < 0.05$), as a possible other manifestation of generalized vasculopathy. There were trends of longer disease duration and higher frequency of anti-topo I antibodies in patients with DUs ($P = 0.09$ and $P = 0.15$, respectively).

Internal organ involvement

Patients with a history of or present DUs had a higher frequency of oesophageal manometry abnormalities only (21/25, 84%, $P < 0.01$). When patients with history of DUs and patients with active DUs were compared with patients without DUs, this association remained significant ($P = 0.01$ and $P < 0.05$, respectively). The whole cohort of 110 patients was then divided into four groups according to the presence of pulmonary involvement (pulmonary fibrosis or ground glass areas on chest HRCT with or without a reduction of DL_{CO} $<80\%$) and/or gastrointestinal involvement (dysfunctional oesophageal lower sphincter on manometry with basal low pressure <15 mmHg) as follows: patients without gastrointestinal or pulmonary involvement (23/110, 20.9%), patients with pulmonary involvement but without gastrointestinal disease (27/110, 24.5%), patients with gastrointestinal involvement but without pulmonary disease (30/110, 27.3%) and patients with gastrointestinal and pulmonary involvement (30/110, 27.3%) [11]. DUs were not seen in the group without internal involvement, while they were present in the second (4/27, 14.8%), third (13/30, 43.3%) and fourth groups (8/30, 26.6%). In addition, DUs showed a statistically significant association and correlation with gastrointestinal involvement ($P < 0.01$; see Table 2).

Discussion

It is well known that behind RP there frequently hides SSc and therefore a thorough internal organ investigation is mandatory [11]. This single-centre study identifies a large cohort of VEDOSS patients in which DUs and asymptomatic or subclinical involvement of the lung and/or gastrointestinal systems are already present. The results are in line with previous studies, confirming not only that early internal organ involvement can be detected in very early SSc patients [7, 12], but also that its prevalence is comparable to what was reported for established SSc patients in a recent meta-analysis [13]. Furthermore,

Table 1 Characteristics of the VEDOSS patients included in this study

	(A) No DUs ($n = 85$)	(B) History of DUs ($n = 9$)	(C) Active DUs ($n = 16$)	*P*-value A *vs* (B + C)	*P*-value B *vs* (A + C)	*P*-value C *vs* (A + B)
Age, mean (S.D.), years[a]	50.9 (16.4)	58.6 (17.7)	47.4 (9.5)	0.87	0.13	0.99
Disease duration, mean (S.D.), years[a]	7.1 (7)	9.6 (6.9)	8.9 (6.2)	0.18	0.35	0.39
Male, *n* (%)[b]	6 (7)	0 (0)	3 (19)	0.68	>0.99	0.13
ACA[b]	44 (52)	4 (44)	11 (63)	0.50	0.73	0.28
SCL70[b]	19 (22)	2 (22)	0 (0)	0.15	0.68	**<0.05**
U1RNP[b]	3 (4)	0 (0)	0 (0)	>0.99	NA	NA
PM-Scl[b]	1 (1)	0 (0)	0 (0)	>0.99	NA	NA
Oesophageal symptoms[b]	40 (47)	5 (56)	10 (63)	0.36	>0.99	0.41
Numbness[b]	15 (18)	8 (22)	4 (25)	0.56	0.68	0.50
Dyspnoea[b]	11 (13)	1 (11)	1 (6)	0.73	>0.99	0.68
Telangiectases[b]	3 (4)	3 (33)	2 (13)	**<0.05**	**<0.05**	0.33
ILD on HRCT[b]	27 (32)	5 (56)	7 (44)	0.16	0.27	0.57
$DL_{CO} < 80\%$[b]	36 (42)	6 (67)	9 (56)	0.17	0.29	0.43
Abnormal oesophageal manometry[b]	39 (46)	9 (100)	12 (75)	**<0.01**	**0.01**	**<0.05**
NVC normal[b]	29 (34)	0 (0)	1 (6)	**<0.01**	NA	0.11
NVC early pattern[b]	31 (37)	8 (89)	11 (69)	**<0.01**	**<0.05**	0.06
NVC active pattern[b]	25 (29)	1 (11)	4 (25)	0.32	0.27	0.77
NVC late pattern[b]	0 (0)	0 (0)	0 (0)	NA	NA	NA

VEDOSS: very early SSc; DUs: digital ulcers; SCL70: anti-topo I antibody; U1RNP: anti-ribonucleoprotein U1; PM-Scl: anti-PM-Scl antibody; ILD: interstitial lung disease; HRCT: high-resolution CT; DL_{CO}: diffusion capacity of carbon monoxide; NVC: nailfold videocapillaroscopy; NA: not applicable. [a]Mann–Whitney *U*-test. [b]Values given as *n* (%). Prevalence determined by chi-square test with Fisher's exact test when appropriate. Values in bold are statistically significant with $P < 0.05$.

Table 2 Risk of organ involvement in patients with DUs

	DUs ($n = 25$), *n* (%)	No DUs ($n = 285$), *n* (%)	Relative risk	*P*-value[a]
No organ involvement	0 (0)	23 (27)	0.00	**<0.01**
Gastrointestinal involvement only	13 (52)	17 (20)	**2.60**	**<0.01**
Pulmonary involvement only	4 (16)	23 (27)	0.59	0.30
Gastrointestinal and pulmonary involvement	8 (32)	22 (26)	1.23	0.61

[a]DU *vs* no DU, chi-squared or Fisher's test when appropriate. Values in bold are statistically significant with $P < 0.05$. DU: digital ulcers.

our data show that DUs are already present in those VEDOSS patients who already show asymptomatic or subclinical oesophageal and/or lung involvement.

The detection of DUs in VEDOSS patients suggests that microvascular abnormalities are already prominent before the fibrotic features of SSc-related cutaneous, gastrointestinal and pulmonary involvement become symptomatic and clinically evident [12, 14]. In our VEDOSS population, a significant association was seen between DUs and anti-topo I autoantibodies, but not between DUs and ACA. This result is partially concordant with previous published data on established SSc patients [15, 16]. Regarding NVC, it is interesting to note that in our single-centre study, no patient with a DU showed a late scleroderma pattern, which is more frequently associated with the presence of peripheral vascular lesions in established SSc patients [17–19]. The evidence that a large number of VEDOSS patients develop internal organ involvement strongly suggests that these patients can be classified as already in an early phase of the disease, despite the

absence of skin tightness, as previously defined by our group [1]. The small number of VEDOSS patients without internal organ involvement may represent a limitation in this study. However, the fact that DUs are absent in patients classified as VEDOSS without organ involvement but present in patients with gastrointestinal and/or lung involvement suggests that DUs may be considered, in some cases, a sentinel sign for evolution from very early to early SSc with internal organ involvement (dysfunctional lower oesophageal sphincter, ground glass on HRCT, DL_{CO} reduction on pulmonary function tests) [1].

In conclusion, while RP remains the main clinical sentinel sign for the suspicion of very early SSc [2, 11], our data suggest that in VEDOSS patients DUs may serve as a clinical sentinel sign of possible internal organ involvement, characterizing evolution to early SSc [1]. It remains to be evaluated how much the new ACR/European League Against Rheumatism (EULAR) criteria will modify the approach to the very early and early diagnosis of SSc now that fingertip ulcers have been added as a classification criterion [20]. It is interesting to note that 44% of the VEDOSS population already fulfil the new 2013 ACR/EULAR classification criteria [9] and further evaluation of and attention to the presence of DUs could improve our ability to diagnose patients as SSc, especially for those patients without a positive disease-specific antibody. However, the VEDOSS study, characterized by diagnostic and not classification criteria, will help determine on a larger number of patients the real position of DUs in the identification of very early SSc and internal organ involvement.

Rheumatology key messages

- Digital ulcers are a major complication in SSc, even in very early and early disease.
- The presence of digital ulcers in very early SSc patients should raise suspicion of internal organ involvement.

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Clinical vignette

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MRI myositis sine myositis: the importance of the histopathology

Sir, A 67-year-old woman complained of painful, swollen ankles that limited weight bearing. Serum inflammatory markers were increased. A US ruled out joint effusion. The MRI scan (Fig. 1, left; coronal and axial views) revealed increased signal intensity in T2 fat-saturated sequences involving both leg muscles diffusely, characteristic of myositis. However, there were no proximal muscle symptoms and creatine kinase (CK) levels were normal. A muscle biopsy was performed (Fig. 1, right; haematoxylin and eosin stain). Remarkably, the muscle fibres showed no necrosis, atrophy or inflammation within the endomysium or in the perifascicular compartment. Conversely, marked inflammatory infiltrates involved the medium to small vessels with fibrinoid necrosis and lumen obliteration; no giant cells or granuloma were present. These findings were consistent with PAN.

MRI muscle oedema may be the result of inflammatory myopathies, infections, trauma, muscle infarction or denervation [1]. Vasculitis is not usually included in the differential diagnosis, making histopathological confirmation essential. PAN restricted to the lower limbs was reported to show a focal, patchy muscle involvement on the MRI [2], whereas in our case the oedema was diffuse (myositis-like). The absence of muscle fibre necrosis in the biopsy explained both the normal CK levels and the preserved strength.

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Fig. 1 MRI and biopsy findings of PAN limited to lower limbs