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ORIGINAL ARTICLE

Ultrasound characterization of cutaneous ulcers in systemic sclerosis

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Abstract

Skin ulcers in scleroderma (SSc) patients are considered a major challenge, both in clinical assessment and treatment decisions. The objective of our study is to assess ultrasonographic (US) morphology of skin ulcers in SSc patients and evaluate if US will be of value in enhancing our clinical information and influence our management plans. We examined a convenience sample of 21 skin ulcers reported in 10 SSc patients by US. We used a previously published US definition of normal skin and developed a preliminary US definition of skin ulcer. Skin ulcers were evaluated by gray scale (GS) and power Doppler (PD) and separated into ulcer and non-ulcer lesions; pain and ulcer measures were obtained using visual analogue scales (VAS). Lesions were characterized and ulcers were clinically and sonographically measured. Ten patients presenting with 21 skin lesions were examined by US. Applying our US definition of skin ulcer, all ulcers were available to measure by ultrasound. Eight lesions were sonographically defined as ulcers, and 13 lesions as non-ulcer lesions. Three ulcers had high PD signals suggestive of infection requiring antibiotic treatment and were monitored for 2 weeks showing a decrease of the pain, VAS, and PD signals. Five lesions showed subclinical calcinosis. This is the first study to show the promising role of US in defining skin ulcers of SSc patients. US may support the assessment of morphology and extent of skin ulcers in SSc and can be a helpful tool for detecting underlying pathology.

Keywords Scleroderma · Skin imaging · Skin ulcers · Skin ultrasound · Ultrasound · Ultrasound dermatology · Ultrasound morphea

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Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease with multiple phenotypic presentations, driven by the interplay of autoimmunity and vasculopathy with excessive dermal and internal organ fibrosis. Microvascular damage is a hallmark in the pathogenesis of SSc, most often manifested clinically by Raynaud's phenomenon, skin ulcers, and pulmonary arterial hypertension (PAH) [1, 2]. Skin ulcers represent a major challenge in SSc, affecting up to 58% of SSc patients and may involve multiple fingers and both hands. Skin ulcers are painful and have a major impact on SSc-related hand disability. SSc patients with digital ulcers (DU) have limited wrist and hand mobility, increased global and hand disabilities, and decreased health-related quality of life compared to those without active DU [3].

Ultrasound (US) is a non-invasive, low-cost, reliable method that has been increasingly used for measuring joint inflammation and damage in rheumatology [4]. It is promising in evaluation of joints and tendons in SSc patients [5]. Additionally, US has been reported to support the assessment of skin thickness in SSc patients [6]. However, there are no previous reports using ultrasonography to evaluate skin ulcers in SSc patients.

Clinical assessment of skin ulcers by visual examination is commonly associated with limited ability to assess the depth of the ulcer, the degree of tissue loss, the presence or absence of underlying calcinosis, and whether the ulcer is infected or not. Skin ulcer is defined histologically as a break in the epithelial integrity of the skin which may extend to deeper structures [7]. Recently, a preliminary clinical definition of skin ulcer in SSc has been developed [8]. US scanning of skin ulcers may provide a unique opportunity to better define and assess skin ulcers. To date, there has been no sonographic characterization of SSc-related skin ulcers. The availability of an objective US image of skin ulcers in SSc may have utility in clinical trials to objectively assess ulcer morphology, extent, severity, and response to treatment. It may also be useful to define and measure skin ulcers in the clinical setting.

The purpose of our study was to preliminarily evaluate the ability of ultrasound (both gray scale (GS) and power Doppler (PD)) to define the morphology and extent of cutaneous ulcers in SSc patients.

Methods

Patients

We examined 10 SSc patients who met 2013 EULAR/ACR criteria for SSc [9] and presented with skin ulcers as clinically diagnosed by rheumatologist. The study was approved by the University of California, Los Angeles Institutional Review Board (IRB).

Ultrasound criteria for defining ulcers and non-ulcers

Skin ulcer is defined histologically as a break in the epithelial integrity of the skin which may extend to deeper structures [7]. Normal skin US was previously described by Wortsman [10]; the author clearly emphasized the sonographic appearance of the skin layers of normal skin (Fig. 1). Skin lesions were separated according to sonographic criteria into ulcer and non-ulcer lesions and the lesions categorized as ulcers were clinically scored and measured on ultrasound.

Ulcers

By GS, a gray scale skin ulcer (GS-SU) was defined as (a) focal loss of epidermis and/or partial dermal loss or (b) focal loss of the epidermal layer and/or partial dermal loss and replacement by irregular hyperechoic tissue located below the level of the surrounding normal epidermis. (Figs 2 and 3).

Non-ulcers

Gray scale non-ulcer lesions (GS-NUL) were lesions of the epidermal layer which may appear as irregular hyperechoic tissue at the same or above the level of the surrounding normal epidermis (Figs. 4 and 5). PD signal was registered in the adjacent tissue to the ulcer. Calcinosis was defined as hyperechoic foci with or without posterior acoustic shadowing [11].We further evaluated calcinosis using PD.

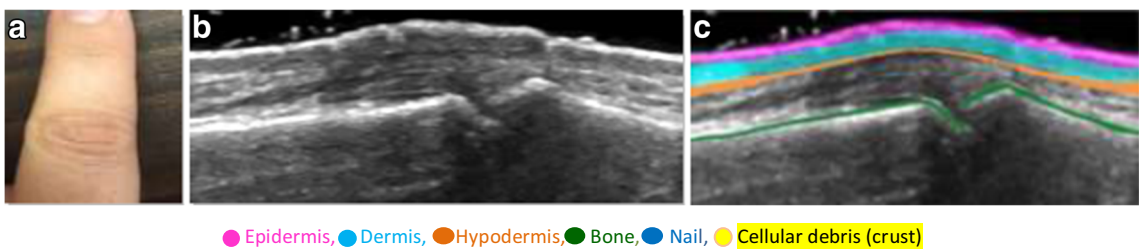

Fig. 1 **a** Clinical image of normal skin overlying proximal interphalangeal joint. **b** Sonography of normal skin overlying PIP with linear probe 15 MHz. **c** Colored figure of normal skin (epidermis, dermis, and hypodermis)

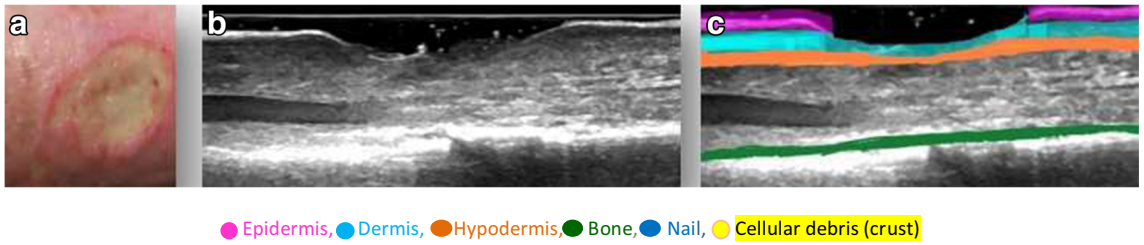

Fig. 2 **a**Clinical image of skin ulcer. **b** Sonography of an ulcer: loss of both dermis and epidermis. **c** Colored figure showing of loss of epidermis and partial dermis

Clinical scoring of ulcers

Clinically, ulcers were measured using a measuring tape (in mm, and surface area calculated by multiplying maximum length and maximum width) in two perpendicular axes and registered in a digital camera image (Sony, 12.1 megapixels, autofocus, digital zoom ×16, with 10–15-cm distance from the ulcer). The overall degree of pain and the effect of finger ulcers on daily activities were evaluated using 100-mm visual analogue scales (VAS), as part of the Scleroderma Health Assessment Questionnaire (SHAQ). The pain VAS question is worded as follows: "How much pain have you had because of your illness in the past week?" The Ulcer VAS question is worded as follows: "In the past week, how much has/have your finger ulcer(s) interfered with your activities?" All clinical, laboratory, and procedural data were obtained from patients' charts.

Ultrasound examination

All ultrasound examinations were performed by one physician who is trained in musculoskeletal sonography. She has more than 2 years of experience using the same equipment (General Electric Health Systems Logic E9, Milwaukee, WI) with a variable frequency linear probe (5–16 MHz). The GS was set for superficial musculoskeletal structures and the PD setting was pulse repetition frequency 800 Hz, frequency 10 MHz, and low wall filter. Patients were seated facing the ultrasonographer; all efforts were made to keep the hand/fingers in zero position. Other scanned areas were fully supported for optimum imaging. A copious amount of gel was placed above the scanned area, creating a pad between the probe and the cutaneous ulcer. Care was taken not to apply pressure on the ulcers so that the patient felt no discomfort.

A sonographic sweep of the lesional and the perilesional areas was performed in two perpendicular planes. Scanning was performed from one ulcer edge towards the center (image to be captured to evaluate maximum depth) and across to the other edge. Depth was measured by having the probe at the point of maximum depth and calculating the depth in relation to the graded line in mm on the side of the captured image (recorded from the epidermal lining to the maximum area of depression in the captured image).

Statistical analysis

A descriptive analysis included means, standard deviations, medians, ranges, and percentages as appropriate. A comparison between GS ulcers and GS-NUL tested using Wilcoxon rank sum test for continuous data and Fisher exact test for discrete data.

Results

Ten patients (nine females and one male), presenting 21 clinical cutaneous lesions (ulcers and non-ulcer lesions), were included. The mean age was 48 (± 17.5) years, mean mRSS is 17.6(± 8.4), and patients' demographics are summarized in Table 1.

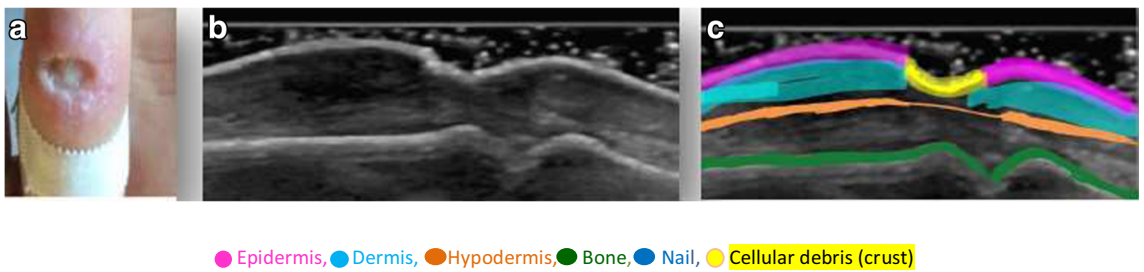

Fig. 3 **a** Clinical image of ulcer showing loss of both epidermis and dermis. **b** Sonography of ulcer showing loss of epidermal layer and replacement by irregular hyperechoic tissue below the level of surrounding epidermis. **c** Colored figure with a yellow depression representing irregular hyperechoic tissue, depressed below the level of surrounding epidermis

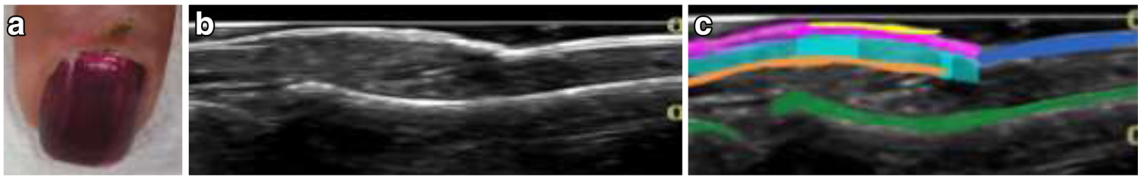

Fig. 4 **a** Clinical image of non-ulcer with slight peripheral depression. **b** Sonographic image showing hyperechoic tissue on top of the epidermis at the center of the lesion. **c** Colored figure showing yellow tissue on top of the epidermis

Ulcer/non ulcers

Sixty-seven percent (67%) of cutaneous lesions (ulcers and non-ulcer lesions) were located on the dorsal aspect of proximal interphalangeal joints (PIPs), two (9%) on the anterior aspect of the legs, one (4%) on the distal interphalangeal joints (DIPs), and three (14%) on posterior aspects of the elbows. Variable depth mean 1.8 mm (SD ± 1.3) was measured by having the probe in the center of the ulcer. Variable dimension mean surface area 100.5 mm^2(SD ± 273) was detected. The main characteristics of ulcers and scars are described in detail in Supplementary Table 1.

We utilized the above proposed preliminary ultrasonographic definition of an ulcer. Eight (8) GS-US ulcer lesions were defined. The loss of both epidermis and dermis is shown in Fig. 2, or by loss of epidermis, partial dermis, and replacement by irregular hyperechoic tissue located below the level of the surrounding normal epidermis (i.e., depressed below level of surrounding normal skin) (Fig. 3). We identified 13 GS-NUL by ultrasound. They demonstrated no break in the epidermal layer with irregular hyperechoic tissue at the same (Fig. 4) or above the level of the normal surrounding epidermis (Fig. 5).

Differences between ulcer and non-ulcer lesions

We evaluated the difference between GS-SU and GS-NUL both clinically and sonographically to better understand the relevant clinical and imaging features that may help identifying an ulcer. Comparing GS-SU to GS-NUL, the GS-SU demonstrated greater surface area (median 55.5 vs 12 mm^2, $p = 0.032$) and higher ulcer VAS values (median 5.5 vs 2.5 cm, $p = 0.027$). Greater depth (median 2 mm vs 0 mm, p value 0.001) and higher PD signal (found in three patients vs 0, p value 0.001) separated ulcers (GS-SU) from non-ulcers (GS-NUL).

Other features

Calcinosis

Five lesions showed calcinosis in the periphery, on top of the bony margin (Fig. 6) or in the periarticular tissues (Fig. 7). Three of these also showed positive PD signals (Fig. 8).

Pain and ulcer VAS

The highest pain and ulcer VAS were detected in the ulcers (three ulcers in two patients) that showed higher PD signals, presumably with concomitant infection based on the presence of a correlation between PD signal and histologic presence of polymorphnuclear leucocytes as well as the reports of PD signal and infected skin and joints [12–15]. After treatment for 15 days with Ciprofloxacin, the PD signal was reduced (Fig. 9a and b). Pain and ulcer VAS went from 10 to 4 and 5 cm, respectively, in both patients (Table 2).

Discussion

In this study, we present a novel application of ultrasound for assessing the morphology of cutaneous ulcers in SSc. This imaging modality allowed non-invasive detection and measurement of the extent of ulcer abnormalities. The presence of PD signals, implying increased vascularity, can be inferred to be indicators of inflammation or infection in a relevant clinical setting and vascularity could be monitored over time. Potential confounders or findings such as calcinosis were also noted.

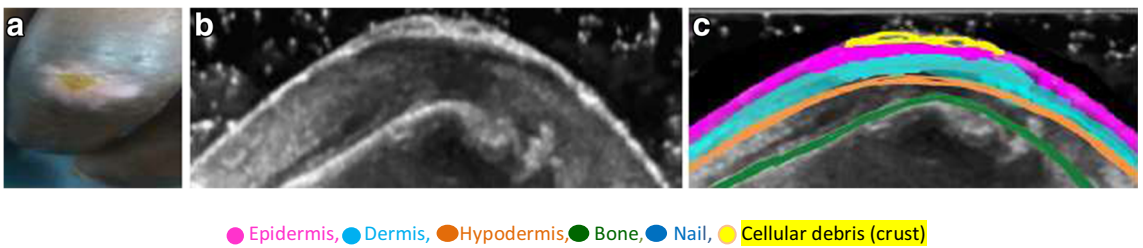

Fig. 5 **a** Clinical image of non-ulcer lesions with irregular skin depression. **b** Sonographic image showing irregular hyperechoic tissue above the level of surrounding epidermis. **c** Colored figure showing irregular yellow tissue above the level of epidermis

Table 1 Demographics, clinical measures, and ulcer characteristic of our systemic sclerosis patients

Variable	(*N*) Mean ± SD or %
Age (years)	(10) 48 (± 17.5)
Females	(9) 90%
Diffuse SSc Subtype	(8) 80%
ILD	(8) 80%
PAH	(2) 20%
Disease duration	(8) 11.6 ± 6.8
MRSS (0–51)	(8) 17.6 ± 8.4
GIT VAS (1–10 cm)	(7) 1.07 ± 1.67
Patient global (1–10 cm)	(7) 6.57 ± 3.21
FVC	(8) 65.5 ± 30.0
Pain VAS (1–10 cm)	(10) 5.70 ± 3.06
Ulcer VAS (1–10 cm)	(9) 4.94 ± 3.49
Calcinosis skin ulcer/lesion	(5) 23%
PD signal in subcutaneous tissue	3(14.2%)

ILD: interstitial lung disease by HRCT, PAH: pulmonary artery hypertension by right heart catheterization, MRSS: modified Rodnan skin score, GIT: gastrointestinal, VAS: visual analogue scale, FVC: forced vital capacity, PD power Doppler

The ability of ultrasound to detect of discontinuity of the epidermis and dermis, together with PD signal which implies the possibility of infection can help guide clinical decisions and have a significant impact on patient pain and ulcer-related disability. The decrease of pain and ulcer VAS in our study demonstrated the potential importance of such a modality in ulcer clinical assessment and outcome.

PD signal reflects increased vascularity and correlates with tissue infiltration with polymorphonuclear leucocytes [12]. Thus, implementing PD evaluation in sonographic assessment of clinical ulcers may be of clinical value. Evaluation of infection by ultrasound was reported in diabetic bone lesions by GS; Enderle et al. [13] reported that GS ultrasound might detect chronic osteomyelitis in the diabetic foot more accurately than conventional radiography. Although PD was not used in the Enderle et al. study, GS ultrasound was similar to bone scintigraphy in detecting diabetic osteomyelitis. MRI (magnetic resonance imaging) was as good as, or superior to, conventional radiography, bone scintigraphy, or ultrasound. Arslan et al. [14] evaluated the efficacy of PD in detecting hyperemia around soft tissue abscesses in comparison

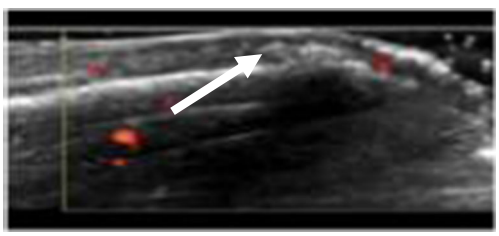

Fig. 6 Calcinosis (white arrow) on top of the bony margin

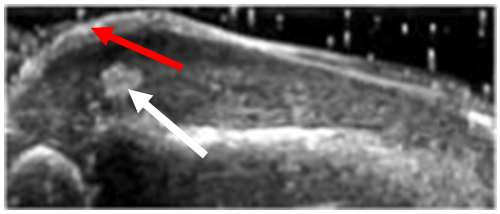

Fig. 7 Calcinosis (white arrow) in the periarticular region; red arrow shows the overlying non-ulcer lesion (red arrow)

to CT (computed tomography) with intravenous contrast being the area of hyperemia detected by PD similar to CT. The authors concluded that PD can be used to assist the diagnosis of superficial soft tissue abscesses. Additionally, Collado et al. [15]reported two cases of pediatric knee infection showing higher PD in the infected compared to the uninfected knee. Our cases support the role of PD to help diagnose superficial infections, this time in SSc-related ulcers. It directs attention towards a possible role for PD in evaluation of infection in skin ulcers.

Calcinosis is a hard-to-treat manifestation of scleroderma and multiple imaging tools have been utilized to identify and quantify calcinosis [16]. It has previously been described by ultrasound [11, 17]. PD signals might suggest inflammation around the deposited calcium, as calcium might be a chronic irritant. However, twinkling artifact attached to calcium deposits has been described in the literature. This artifact occurs in the presence of highly reflective calcified objects such as calculi and is not thought to reflect inflammation. The latter artifact is usually dependent on the machine setting and should be managed by the operator [18]. On the other hand, calcium deposits with PD signal might actually reflect inflammation and thus be amenable to treatment with anti-inflammatory medications, based on data demonstrating that the degree of subsynovial polymorph-nuclear leucocytes correlated significantly with the degree of PD signal in joints [12]. Further research is needed to investigate this attribute.

We assume that the irregular hyperechoic tissue present in the cutaneous lesions represents cellular debris, re-epithelization, and/or crust; there was no histological confirmation because a biopsy was not medically indicated in these cases.

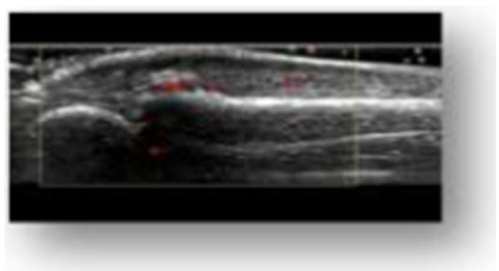

Fig. 8 Power Doppler signal (white arrow) underneath the calcinosis

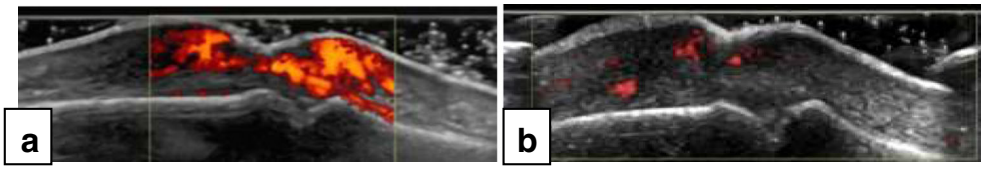

Fig. 9 **a** Skin ulcer with high PD signal in the subcutaneous tissue, before antibiotic treatment

Moreover, the latter invasive procedure may injure the tissue, interfering with healing.

Management of skin ulcers in SSc is multifactorial, requiring patient education and non-pharmacological interventions (maintain a warm core body temperature, cessation of smoking). Pharmacological therapies are available which may prevent SSc-related skin ulcers (e.g., phosphodiesterase type-5 inhibitors) or treat them (e.g., i.v. iloprost), thus making accurate diagnosis of skin ulcers even more useful [19, 20].

The use of US to define and follow skin ulcers in SSc may have a significant role in clinical research. Previous trials attempting to show that skin ulcers may be improved with therapy have failed to show any evidence of healing [21]. This may well have been because the outcome measure, clinical ulcers, has been poorly defined. US has the potential to objectively characterize and monitor skin ulcers in SSc and thus become a more reliable and sensitive tool than clinical evaluation alone. This, in turn, can lead the way to effective therapy, improving the health and sense of well-being of SSc patients with this painful and disabling condition.

Our study has some limitations, one limitation was the small number of cases; however, 10 cases represented 21 lesions, eight of them ulcers by ultrasonography. In our study, the relatively small number of patients precluded formal statistical correlations between skin ulcers and other aspects of disease, although the literature supports correlations between skin ulcers, ILD, and disease subsets [22]. Our study could not examine the predictive value of these ultrasound lesions, as our study was cross-sectional. Videocapillaroscopy predicted ulcers based on the mean number of capillaries per millimeter in the middle finger of the dominant hand; however, the ulcers were not defined or corroborated by imaging of the actual ulcer [23]. While our ultrasound study is a step towards defining ulcers in a more objective manner, this methodology will need formal validation and an ultrasound scoring system to monitor the healing, or worsening, of ulcers would be useful. These steps will be undertaken in the future.

Table 2 Clinical and ultrasonographic difference between gray scale skin ulcer and non-ulcer lesions

	Ulcers GS-SU (total 8)	Non-ulcers GS-NUL (total 13)	*p* value
Clinical: surface area (mm)	55.5 (16.5–160.6)	12.0 (4.0–16.0)	0.032*
Pain VAS (0–10 scale)	6 (6.9–10.0)	7 (3.0–7.0)	0.455
Ulcer VAS (0–10 scale)	5.5 (5–9.6)	2.5 (2.8)	0.027*
Ultrasound: depth (mm)	2 (0.75–3.0)	0	< 0.001*
Power Doppler Y/N	3 (yes) 5 (no)	13 (no)	0.042*
Calcinosis Y/N	8 (no)	8 (no), (5 yes)	0.111

Conclusion

For the first time, we show preliminary data to support the use of ultrasound in evaluation of the morphology and extent of skin ulcers in SSc and point to the possibility that it may be used to guide therapy. We also describe the need to further validate this methodology.

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Compliance with ethical standards

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