Rheumatology: Current Research

Li et al., Rheumatology (Sunnyvale) 2016, 6:3
DOI: 10.4172/2161-1149.1000202

Short Communication Open Access

We can't Treat Scleroderma Skin Ulcers if we can't identify them

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Received date: July 05, 2016; **Accepted date:** July 25, 2016; **Published date:** July 28, 2016

Commentary

Systemic sclerosis (SSc) is a complex autoimmune disease that can involve a number of organs including skin, lung, heart, kidneys and the gastrointestinal tract. Among these, digital ulcers (DU) continue to be a source of pain, disability, and hospitalization. In an observational cohort study of 189 SSc patients identified from the EUSTAR database, patients with at least 1 DU reported 20% greater impairment in daily activity compared to patients without any DU [1]. Digital ulcers can also occasionally become life threatening, as gangrene and sepsis can occur. Out of the 2080 SSc patients identified in the Pittsburgh Scleroderma Database, 58% of patients had experienced at least 1 DU while 9.5% of patients experienced severe complications such as gangrene or the need for amputation or sympathectomy [2].

Digital ulcers are important factors impacting the lives of patients with SSc [3]. The prevalence of DU is quite variable ranging between 8-50% [4-7]. This variability may be caused, at least in great part, by a lack of a uniform definition of SSc-DU. A recent systematic literature review winnowed 3464 citations down to 66 articles including any studies that attempted to define skin ulcers among patients with SLE, RA, vasculitis, SSc, other connective tissue diseases, or diabetes [8]. An amazing 79 different ulcer definitions were found, including phrases such as "loss of epidermis", "loss of epidermis and dermis", "denuded", "with depth." In addition, a number of uncorrelated and nonspecific definitions such as "open sore," "skin break," and etc were found. This clearly documents the lack of a consistent, validated measure of skin ulcers in systemic sclerosis.

Obviously, lesions such as abrasions, which affect only the epidermis, will not respond to treatment equally compared to a lesion penetrating the basement membrane of the dermis. Furthermore, the etiology of the lesion, such as underlying calcinosis, arteriosclerosis, vasculitis, and infection, may influence responsiveness. Different clinicians may recognize different lesions as "DU," resulting in great inconsistencies in therapy and outcome. As such, the lack of a uniform definition not only presents a major challenge for addressing the needs of the individual patient, but also for clinical trials in DUs [9].

Furthermore, the value of a uniform definition is exemplified by the explosion of new therapies for rheumatoid arthritis in the 1990s. Prior to the development of the ACR Response Criteria and the Disease Activity Score, the lack of a generally accepted method for measuring improvement in RA patients prevented accurate statistical analysis and extrapolation of data in clinical trials. The introduction of the ACR Response Criteria served as a statistically powerful tool that improved existing methods to measure primary efficacy by excluding a large percentage of placebo patients as being improved [10]. In conjunction with the technology to manufacture new therapies, the development of a single definition of improvement facilitated the rapid expansion of effective therapies for rheumatoid arthritis and significantly improved the quality of life of thousands of RA patients [11].

Although significant work has been done examining the skin in scleroderma and ultrasound systems to score the skin overall have been developed, this is NOT true when it comes to skin ulcers per se [12,13]. This clear need has led to some recent attempts to define SSc DU. Baron et al and the World Scleroderma Congress have offered consensus-derived definitions of digital ulcers (Table 1) [14]. However, both of these are purely clinical. A more objective measure needs to be developed and compared to the clinical measures.

	DU Definition
Baron et al. [14]	A lesion with visually discernable depth and a loss of continuity of epithelial coverage, which could be denuded or covered by a scab or necrotic tissue.
World Scleroderma Congress [15]	A loss of epidermal covering with a break in the basement membrane (which separates dermis from the epidermis). It appears clinically, or would appear after debridement, as visible blood vessels, fibrin, granulation tissue, and/or underlying deeper structures (e. g. muscle, ligament, fat).

Table 1: Baron et al and the World Scleroderma Congress have offered consensus-derived definitions of digital ulcers.

Recently, Suliman et al. examined 21 ulcers in 10 SSc patients and found that there was only a 48% concordance between clinical and ultrasound examination for ulcers [8]. Aliano et al. examined 20 patients clinically diagnosed with superficial sacral ulcers (National Pressure Ulcer Advisory Panel Stage I/II) and found that all 20 patients, in contrast, demonstrated evidence of deep tissue injury upon ultrasound examination rather than superficial injury [16]. Just as with Suliman et al., ultrasound and clinical evaluation were very different. The application of ultrasound in ulcer classification may provide us with the objective measure of skin ulcers.

So why is this of any interest?

First, only when an ulcer can be reliably defined, can one accurately assess treatment efficacy. Not only is this issue relevant to SSc DU, it is also important for the treatment of ulcers of other etiologies [16,17].

Second, with the advent of new and effective therapies for finger/hand/arm skin ulcers in SSc, rheumatologists will be able to more effectively treat these patients on a clinical basis, improving their quality of life and, occasionally, forestalling hospitalizations, amputations, and even sepsis.

Third, a history of digital ulcers is associated with worse prognosis, making DU an important predictor that will allow risk stratification of SSc patients [18]. Initiation of early treatment for high-risk patients can help delay cardiovascular deterioration and improve disease outcome.

Fourth, using ultrasound in a new and novel way to measure skin ulcers further enhances the value of ultrasound and may expand its uses in the future.

In summary, it is time to develop a sensitive, reliable, and potentially more objective measure of SSc-skin ulcers to help improve therapy and patients' quality of life.

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