Scientific Research Publishing

Open Journal of Rheumatology and Autoimmune Diseases, 2022, 12, 35-45
https://www.scirp.org/journal/ojra
ISSN Online: 2164-005X
ISSN Print: 2163-9914

Lower Extremity Ulcers in Patients with Systemic Sclerosis

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How to cite this paper: Bean, M.B. and Derk, C.T. (2022) Lower Extremity Ulcers in Patients with Systemic Sclerosis. *Open Journal of Rheumatology and Autoimmune Diseases*, **12**, 35-45.
https://doi.org/10.4236/ojra.2022.121005

Received: January 18, 2022
Accepted: February 22, 2022
Published: February 25, 2022

Abstract

Introduction: Cutaneous manifestations of systemic sclerosis (SSc) include skin ulceration; 4% - 12% of patients with SSc develop lower extremity ulcers of various etiologies. Limited data, significant morbidity, and substantial cost of wound care led us to undertake this study to describe and identify risk factors. *Methods*: After Institutional Review Board approval, we identified 30 patients with SSc and lower extremity ulcers over a 10-year period at a single center with an SSc clinic, which were included in a descriptive analysis. *Results*: Median age of onset of lower extremity ulcers was 59.5 years (range 20 - 84). Ninety percent of patients were female, 60% were Caucasian, 63% had limited SSc, 13% diffuse SSc and 23% an overlap syndrome. Immunomodulators or steroids were prescribed in 53%; hypercoagulable state identified in 16%. Ulcers were attributed to venous stasis (27%), SSc (20%), trauma (20%), arterial disease (17%), and multifactorial/unknown (17%). In patients with ulcers attributed to SSc, age at onset was lower (45.5 vs 59.5 years). Biopsies generally did not contribute to management. Multidisciplinary treatment was routine; 20% required amputation, 10% endovascular intervention, 20% frequent surgical debridement, 10% hyperbaric oxygen, 26% local treatment and antibiotics and 13% received immunosuppression for wound treatment. *Conclusion*: Lower extremity ulcers are a serious clinical problem in patients with SSc. The clinical exam, venous dopplers, ankle-brachial indices and assessment of vascular risk factors helped define causality. In younger patients, ulcers were more frequently attributed to SSc and these patients were more likely to be on immunosuppressants/DMARDS, possibly indicating severe phenotype of SSc.

Keywords

Lower Extremity Ulcers, Systemic Sclerosis, Scleroderma, Peripheral Vascular Disease, Venous Stasis

1. Background

Systemic sclerosis (SSc) is an autoimmune rheumatic disorder characterized by vascular dysfunction, cutaneous and visceral organ fibrosis, and characteristic autoantibodies [1]. Common cutaneous manifestations of disease activity include skin thickening, Raynaud's phenomenon, and digital ulceration [2]. Lower extremity ulcers are significantly less common than these other cutaneous manifestations and as such, are less well understood and less described in the literature. Based on small studies and case reports, the estimated prevalence of lower extremity ulcers is approximately 4% - 12% among patients with SSc [3] [4]. Not much is known regarding demographic findings, risk factors, and effective treatment modalities for patients with SSc and lower extremity ulcers.

The small amount of literature available suggests that the causality of lower extremity ulcers in patients with SSc is multifactorial, such as arterial, venous or neurotrophic in origin. Additionally, in the SSc population, pure ulcers, or those with morphologic characteristics of arterial ulcers but without evidence of arterial insufficiency, have been attributed to SSc related microvascular changes. Based on prior studies, the only yet identified risk factor for these pure ulcers is personal history of lower extremity ulcer [5]. Given the significant morbidity that all lower extremity ulcers pose to patients, it is important to identify further risk factors for development of ulcers to aid in prevention.

The literature with regards to lower extremity ulcers in patients with SSc hypothesizes that the patients are more likely to have prothrombotic genetic mutations, which may lead to a predisposition to lower extremity ulcers [3]. In these cases, treatment with anticoagulation has demonstrated to be an important component of therapy. In general, understanding all comorbidities in patients with ulcers and SSc is important to formulate an effective treatment plan. A study in Japan in patients with SSc, pulmonary arterial hypertension and non-digital ulcers demonstrated that bosentan was effective in treating ulcers [6].

Care for leg ulcers often requires a multidisciplinary team of dermatologists, surgeons and wound care nursing specialists for effective wound healing. Wound healing can also often take months to years depending on the etiology of the wound, the vascular supply, and patient's comorbidities. Patients often try many different interventions prior to successfully treating the wound. Patients with SSc often take many medications for disease control as well as symptom management. Steroids, in particular, are critical in some patients with autoimmune disease, but can be detrimental to wound healing, complicating treatment of these ulcers. It is important to understand how medical treatment of lower extremity wounds fits with SSc treatment.

The cost of wound related medical expenses is substantial; a study of Medicare beneficiaries estimated that in 2014, the estimated mean Medicare spending for wound care per beneficiary was on average $5003 for chronic ulcers, $2054 for venous wound, and $13,571 for arterial ulcers [7]. Learning more about effective

options for wound treatment in this population can help decrease the cost to the healthcare system as well as the substantial psychological and time costs to patients.

The purpose of this investigation is to further characterize demographics, risk factors, and treatment modalities of the poorly understood topic of lower extremity ulcers in SSc that causes considerable morbidity for patients.

2. Methods

The Institutional Review Board at the University of Pennsylvania approved the study.

The study employed the electronic medical record (EMR) to identify all patients over 18 years of age at the University of Pennsylvania who carry a diagnosis of SSc and lower extremity ulcers over a prespecified time interval. A request was made to the Data Analytics Center (DAC) to pull Electronic Medical Record data for all patients with diagnosis codes for systemic sclerosis (M34.0) and ulcers or wounds on the lower extremity 707.1 (ulcer of lower limb NOS), 707.19 (ulcer other part low limb) 707.11 (ulcer of thigh), 717.12 (ulcer of calf) 707.13 (ulcer of ankle), 707.1 (ulcer of lower limbs, except pressure ulcer), 454.0 (leg varicosity w ulcer), 459.31 (chronic venous hypertension with ulcer). Patients from a 10-year period between July 2010 and July 2020 were included. The search yielded 57 patients. The charts were then individually reviewed to confirm diagnosis of systemic sclerosis and lower extremity ulcers. Twenty-seven patients were removed from the analysis due to improper coding within the electronic medical record or incomplete medical records, and 30 patients were included in chart review. The patients' individual medical records were reviewed to identify predetermined patient demographics, systemic sclerosis features, wound features and treatment details. The data were evaluated qualitatively given their nominal properties.

3. Results

Demographics and patient characteristics:

Thirty patients with systemic sclerosis and lower extremity ulcers were identified (Table 1), the median age of onset of lower extremity ulcer was 59.5 years (range 20 - 84), ninety percent of patients were female and sixty percent were Caucasian, while 37% were African American. The majority of patients, 63%, presented to a physician within 1 month of their wound onset.

Presence of a hypercoagulable state was either clinically suspected based on multiple thrombotic events or confirmed with laboratory testing in 16% of patients.

Regarding comorbidities, 30% had venous hypertension or venous stasis, while 37% of patients had known peripheral arterial disease, which was confirmed with angiography or ankle-brachial index testing. Seven percent had both venous and arterial vascular disease. Sixty percent reported peripheral neuropathy, due to

Table 1. Patient demographics.

Age at onset	59.5 years (20 - 84)	n	%
Sex	Male	3	10%
	Female	27	90%
Race	Caucasian	18	60%
	African American	11	37%
	Unknown	1	3%
Ulcer location	Toes	3	10%
	Feet	4	13%
	Ankle	7	23%
	Leg	11	37%
	Thigh	2	7%
	≥3 sites	5	17%
Ssc Type	Limited	19	63%
	Diffuse	4	13%
	Overlap syndrome/NOS	7	23%
Hypercoagulable state	abnormal antiphospholipid antibodies	4	13%
	Clinical evidence	1	3%
Comorbidities	Raynaud's	27	90%
	Digital ulcers	16	53%
	Osteolysis	9	30%
	Digit loss	7	23%
	Peripheral neuropathy	18	60%
	Diabetes	2	7%
	Hypertension	20	67%
Vascular disease	Venous	9	30%
	Arterial	11	37%
	Venous and Arterial	2	7%
Tobacco use	Current	4	13%
	Former	6	20%
	Never	20	67%
Medications	PD5 inhibitor	11	37%
	ERA	7	23%
	ACE/ARB	8	27%
	Anticoagulation	3	10%

Continued

	Antiplatelet	18	60%
	Calcium channel blocker	25	83%
	Pentoxyphylline	8	27%
	IV prostacyclin analog	2	7%
Immunosuppressant use for Ssc at time of ulcer	Yes	20	67%
	No	10	33%

various etiologies and six percent had diabetes. Most patients, 63%, had never smoked while 67% had documented history of hypertension.

Wound characteristics:

The most common location for wounds were the lower legs including shin and calf (37%) followed by ankles (27%) and sixteen percent had more than 3 different sites on the lower extremities.

The etiology of the ulcers was variable: 27% were thought related to venous stasis, 20% directly related to systemic sclerosis, 20% related to trauma, 17% were attributed to peripheral arterial artery disease, and 17% were thought to be multifactorial, infectious or truly unknown.

Eleven out of thirty patients had biopsies of their ulcers and of the biopsies that were done, four revealed probable/possible active SSc and 1 revealed a vasculopathy.

Features of systemic sclerosis:

Regarding the clinical features of SSc of these patients, 63% of patients had limited scleroderma, 23% had an overlap syndrome, and 13% had a diffuse subtype of SSc.

Nearly all patients who had autoantibodies collected had a positive ANA, the vast majority, 90%, of patients reported Raynaud's phenomenon, while 53% had digital ulcers, 30% had osteolysis and 23% had at least partial digit loss in upper or lower extremities due to their Raynaud's phenomenon.

Interestingly, 53% of patients were on immunomodulators for treatment of their SSc or SSc overlap syndromes. Of these patients, 38% took mycophenolate mofetil, 38% took prednisone, 31% took hydroxychloroquine, and 6% took sulfasalazine, mycophenolic acid, methotrexate, azathioprine or a TNF-alpha inhibitor.

Wound treatment:

The patients generally received multidisciplinary treatment outside of their rheumatologist to treat the lower extremity wounds. Twenty-percent eventually required amputation due to their wounds, ten percent underwent an endovascular intervention to address the wounds, an additional 20% percent required frequent surgical debridement, including 2 patients who underwent donor skin grafting, ten percent underwent hyperbaric oxygen therapy as part of their treatment for the ulcers. Twenty-six percent of ulcers were treated with topical agents,

dressings and antibiotics alone and did not require more aggressive management. A total of 13% of wounds were treated with immunosuppression, biologic agents or steroids.

Regarding other medications that patients used to treat their comorbid conditions: almost all patients, or 83%, were prescribed a calcium channel blocker for the treatment of Raynaud's phenomenon, 60% used aspirin or other antiplatelet medication, 37% used a phosphodiesterase-5 inhibitor, 26% used pentoxyphylline, 26% took an ACE-inhibitor or angiotensin-II receptor inhibitor, 23% took an endothelin receptor antagonist, 10% were systemically anticoagulated with warfarin or a direct oral anticoagulant, and 7% used a prostacyclin analog for treatment of pulmonary arterial hypertension.

Patients with ulcers suspected to be related to systemic sclerosis

Patients with ulcers suspected to be related to systemic sclerosis were further described in Table 2.

Five out of six patients were female. The median age of ulcer onset was 45.5 years. Half of the patients had abnormal findings on hypercoagulable workup. None of the patients required amputation though notably, all patients aside from patient 2 still had ongoing ulceration at the time of this assessment. Patient 2's ulcers resolved with hyperbaric oxygen therapy.

Figures 1-5 depict representative ulcers that were considered to be related to systemic sclerosis based on clinical history and absence of other etiologies.

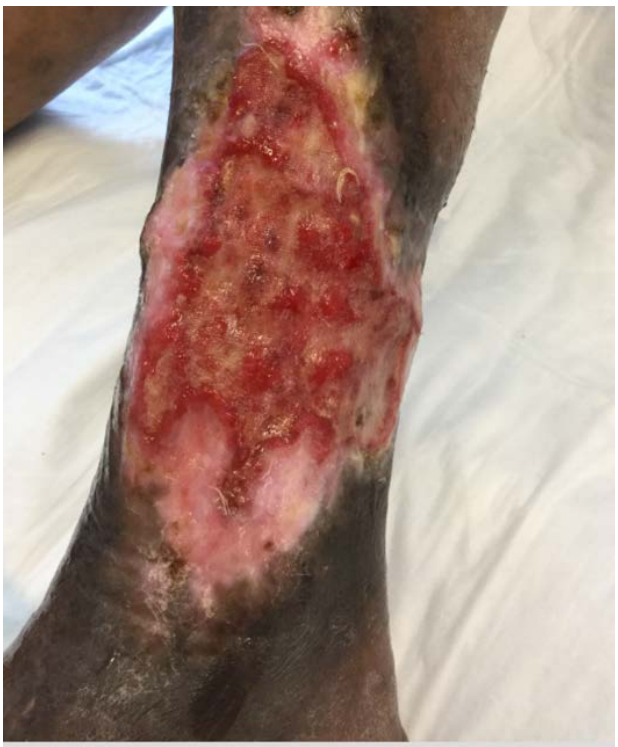

Figure 1. Representative wound, patient 5, a 42-year-old current smoker with SSc and lupus overlap and high titer ANA whose wounds originally appeared at age 33 and have required treatment with multiple rounds of antibiotics and skin grafting.

Table 2. Patients with ulcers attributable to systemic sclerosis.

Patient	1	2	3	4	5	6
Sex	F	F	F	M	F	F
Race	C	C	AA	C	AA	C
Age at Ulcer Onset	58	24	53	38	33	64
Ssc clinical subtype	Limited	Diffuse	SSc/Rheumatoid Arthritis overlap	Limited	SSc/SLE overlap	Limited
Antibodies	ANA + without titer,	ANA 1:1280 diffuse	ANA 1:1280 speckled	ANA 1:640, diffuse	ANA 1:10,240, speckled	ANA 1:640, speckled
	dsDNA 13	Scl 70 6.9	CCP 165	RF 17	+RNP, +Smith, +cryoglobulins +RF	+RNA pol III
Organ involvement	Raynaud's, digital ulcerations, ILD	Raynauds, digital ulcerations, ILD	Raynaud's GERD, arthritis, skin vasculitis	Sclerodactyly	Raynaud's, digital ulcerations, ILD, PAH, pericardial effusion, sclerodactyly, calcinosis, gastric dysmotility, oral ulcers	Raynaud's, digital ulcerations, GERD, sclerodactyly, calcinosis, sicca symptoms
Hypercoagulable state	mildly elevated cardiolipin IgM; homozygous MTHFR mutation (C667T),	Mildly elevated anticardiolipin IgM, upper extremity arterial embolism	None	None	None	mildly elevated protein C, mildly elevated Factor VIII
Vascular disease	Mild PAD	Microvascular disease only	None	None	venous hypertension	None
Hypertension	No	No	Yes	Yes	No	Yes
Diabetes	No	No	No	No	No	No
Ulcer location	Bilateral legs and feet	Bilateral toes	R lateral ankle	L medial ankle	Bilateral lower anterior legs	Bilateral lower anterior legs
Biopsy	Epidermal ulceration with fibrosis and sclerosis. deep dermis with evidence of collagen fiber thickening and sclerosis concerning for persistent ulceration in the setting of systemic sclerosis.	-	No evidence of vasculitis, histology consistent with edge of a wound	-	Medium vessel vasculitis, neutrophilic infiltrate in dermis	Dermal sclerosis and mixed inflammation. Lymphocytic infiltrate. Decreased elastin fiber content in the areas of sclerosis. The sclerosis noted could be consistent with a prior history of scleroderma

Continued

Immunosuppressants	MMF	plaquenil	MTX, SSZ, infliximab, rituximab	None	MMF, plaquenil, prior cyclophosphamide, mycophenolic acid, prednisone (prior to development of wound)	MMF
Ulcer Treatment	Topical only	IV antibiotics, hyperbaric oxygen.	IV antibiotics. Frequent debridement. Rituximab for wound	Frequent debridements. Multiple rounds of antibiotics.	multiple rounds of antibiotics, skin graft, cyclophosphamide, rituximab.	antibiotics mycophenolic acid, pentyoxyphylline for vascular component
Topical treatments	profore wraps, topical gentamycin, unna boot, topical mupirocin	No topical treatments used	collagenase, miconazole, clotrimazole, ammonium lactate	Clobetasol, metronidazole gel, topical mupirocin, santyl, silvadine	wound vac, silicone border, kerlix, and coban, tefla dressing	medihoney, triamcinolone, vaseline gauze

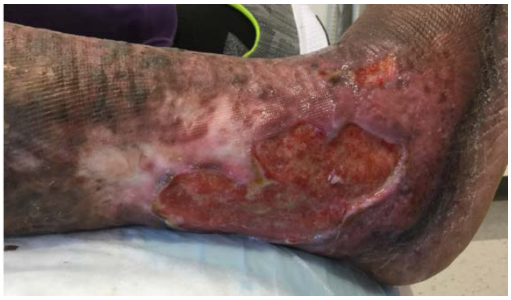

Figure 2. Representative wound, patient 3, a 64-year-old female with SSc/rheumatoid arthritis overlap syndrome whose ulcer appeared at age 53, and has been treated with IV antibiotics, frequent debridement, and rituximab for ulcer.

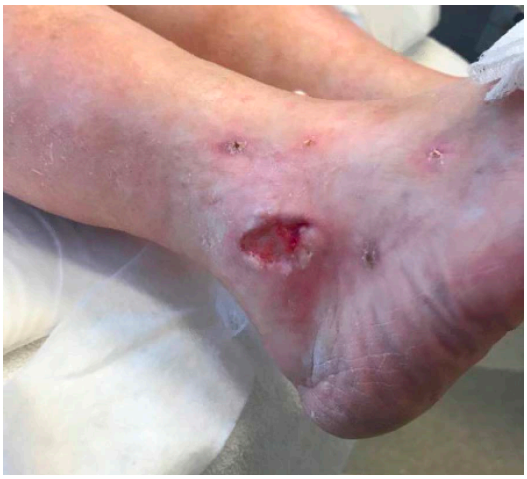

Figure 3. Representative wound, patient 1, a 62-year-old female former smoker with mild peripheral arterial disease whose lower extremity wounds were treated with topical products.

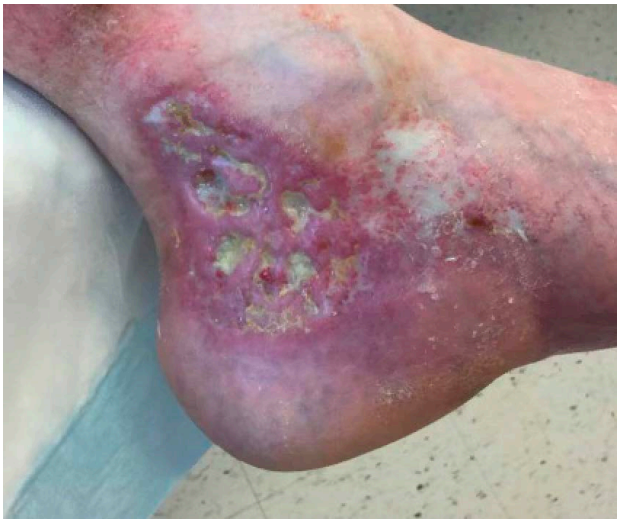

Figure 4. Representative wound, patient 4, a 42-year-old man with hypertension and sclerodactyly with no other vascular risk factors whose wounds were treated with multiple debridements and topical products.

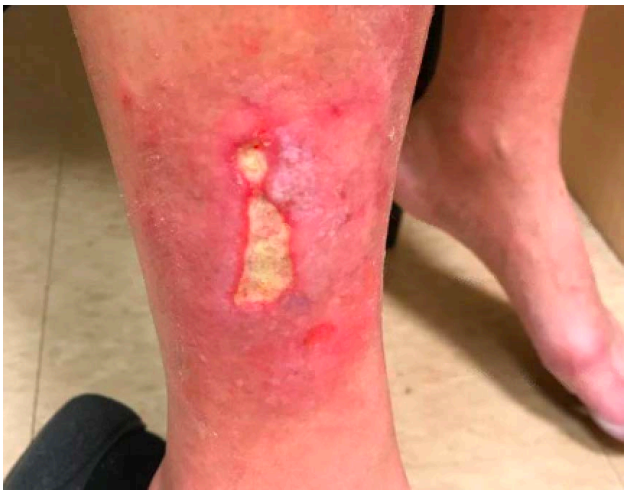

Figure 5. Representative wound, patient 6, a 64 year-old-female whose ulcers were treated with topical products and the vascular component of wound was treated with pentoxyphylline.

4. Discussion

It is clear from our study as well as previous studies that lower extremity ulcers increase morbidity in patients with systemic sclerosis. Once ulcers develop, they often require extensive management that is often not uniform and typically based on the type of ulcer. Twenty percent of patients required amputation and ten percent invasive procedures such as surgical revascularization, vein ablation or endovascular stenting due to non-healing ulcers.

Regarding biopsies, in general, biopsies of ulcers did not often contribute to management. In fact, 36% of biopsies were in the setting of an amputation. Typically, the type of ulcer was elucidated by clinical exam, venous dopplers and ankle-brachial indices, and evaluation of vascular disease risk factors. However,

there were select patients who did not have vascular risk factors and their wounds were felt to be due to microvascular disease related to systemic sclerosis. Many patients were tapered off of steroids and taken off of immunosuppression to promote wound healing, while in rare cases immunomodulators were added as there was suggestion of active SSc skin near the area of the ulcer.

Other studies have suggested that the presence of a hypercoagulable state as evidenced by the presence of antiphospholipid antibodies may contribute to the development of lower extremity ulcers in patients with systemic sclerosis [3]. Our population of patients as compared to previous studies had a lower prevalence of abnormal hypercoagulable studies (only 16%, compared with 50% in other studies). The prevalence in our study is closer to the estimated prevalence of positive anticardiolipin antibodies in the general systemic sclerosis population which is around 3% - 12% [8] [9]. The retrospective nature of this study precluded our ability to have data on all patients regarding antiphospholipid antibodies, but based on other studies, obtaining this information may be helpful in treating ulcers in these patients.

In patients whose wounds were thought to be related to systemic sclerosis, it is notable that the median age of onset of the wound was much lower (45.5 vs 59.5 years) than that of our total population of patients. Although it is difficult to extrapolate from such a small population, it is possible that younger patients are less likely to have accumulated other vascular risk factors such as diabetes, neuropathy, venous hypertension or peripheral arterial disease, and as such, the younger population is more likely to have ulcers attributed to their systemic sclerosis.

In addition, patients with ulcers attributed to scleroderma were more likely (67% vs 30%) to be prescribed immunosuppressants/DMARDs to treat their systemic sclerosis. Perhaps this indicates that these patients have more severe phenotypes of systemic sclerosis at baseline.

There were several limitations to this study. As a retrospective study, it wasn't possible to proactively collect data—as such, some antibodies, including those indicative of hypercoagulable state, were not available. In some patients, medical records from wound care clinics were not fully available and wound care details were extrapolated from pharmacy records or second hand from notes from different specialties that were not specifically wound care. The sample size was small, and there was no comparison group of patients without lower extremity ulcers, making the power to detect meaningful trends difficult.

5. Conclusion

Lower extremity ulcers are a serious clinical problem in patients with SSc. The clinical exam, venous dopplers, ankle-brachial indices and assessment of vascular risk factors helped define causality. Twenty percent of patients required amputation for lower extremity ulcers. In younger patients, ulcers were more frequently attributed to SSc and these patients were more likely to be on immuno-

suppressants and DMARDS, possibly indicating severe phenotype of SSc. Overall, more studies need to be done to better understand the risk factors for developing lower extremity ulcers in SSc which in turn may help us in decreasing morbidity.

Conflicts of Interest

The authors declare no conflicts of interest.

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