Platelet-rich plasma for the treatment of scleroderma-associated ulcers: a single-center experience and literature review

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Abstract

Systemic sclerosis (SS) is a complex connective tissue disease characterized by vasculopathy and progressive fibrosis, primarily considered an autoimmune disorder. SS can affect multiple organs and tissues, including the skin, respiratory, gastrointestinal, genitourinary, cardiovascular, and musculoskeletal systems. Skin involvement is common, and SS-related ulcers, especially digital ulcers, occur in roughly 50% of patients. These ulcers not only cause pain but also significantly impact patients' quality of life, and in severe cases, they can lead to infection, gangrene, and amputation. The search for novel therapies for scleroderma-related ulcers remains an ongoing research area. Platelet-rich plasma (PRP) has been investigated as a potential treatment for difficult-to-heal ulcers, including diabetic, pressure, and vascular ulcers. In this study, we share our experience in treating scleroderma ulcers with PRP. Ten patients with confirmed SS and chronic skin ulcers lasting at least six weeks, which had not responded to conventional treatments, were selected for the study. Homologous PRP gel was prepared and applied once a week for up to eight weeks. The ulcers were documented photographically before and after PRP treatment, and pain levels were assessed using a visual analog scale (VAS). We also conducted a systematic review of the literature focusing on the use of PRP in the setting of SS. The results from our casuistry showed that the ten patients, including eight females and two males with a median age of 52.5 years, had ulcer sizes ranging from 0.78 cm^2 to 28.26 cm^2. The ulcers were located on fingers, legs, and heels, and they were associated with various forms of SS, including limited and diffuse cutaneous involvement. Raynaud's phenomenon was prevalent, and two patients exhibited organ involvement. The average ulcer size at the end of PRP treatment decreased significantly, with a 78% reduction in ulcered area. Pain levels also markedly improved, as indicated by a reduction in VAS scores. With regards to systematic revision of literature, we retrieved 45 cases of SS treated with PRP-based therapeutic regimes. However, only a minority of them (n=16) underwent PRP treatment for the treatment of SS-related ulcers. An improvement in wound size and pain has been documented in all cases. Taken together, these data highlight the potential benefits of using homologous PRP in the treatment of scleroderma ulcers, emphasizing its positive impact on ulcer size reduction and pain relief.

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Introduction

Systemic sclerosis (SS) is a connective tissue disease characterized by a process of vasculopathy and progressive fibrosis. As for the pathogenesis, SS is considered autoimmune disorder. Due to its systemic basis, SS potentially affects all the organs and tissues of the human body, including the respiratory, gastro-enteric, genito-urinary, cardiovascular and musculoskeletal systems.[1] The skin is one of the most frequently involved sites. Skin ulcers, especially digital ulcers, are a frequent complication of SS, occurring in about 50 percent of patients.[2] SS-related ulcers are often cause of pain and represent an important burden in terms of patients' quality of life. In more severe cases, scleroderma ulcers can lead to infection, gangrene and, eventually, amputation.[2] SS ulcers are typically localized at the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints. Lower extremities represent the second most frequent site of occurrence of SS-related ulcers. Several therapeutic strategies have been proposed for the prevention and treatment of skin ulcers in SS. The use of Bosentan, an entodelin-1 receptor antagonist, has been shown to

reduce the incidence of cutaneous ulcers, but has demonstrated little efficacy on promoting healing of pre-existing ulcers. The most widely used therapy for the treatment of ulcers in SS is represented by intravenous prostaglandin analogs (*e.g.*, Iloprost), which has been proven to have even higher vasodilator effects when compared to oral administration.[3] To date, the identification of new therapies is still a growing field of research for patients with scleroderma ulcers. The use of platelet-rich plasma (PRP) has already been described in the literature for the treatment of difficult-to-heal ulcers, including diabetic, pressure, vascular ulcers.[4] PRP is characterized by high concentration of growth factors and cytokines involved in the wound healing process. In the setting of SS, some case reports and small cohort studies indicate the potential effectiveness of PRP for the treatment of cutaneous ulcers (for a detailed overview see the Discussion section). The aim of the present paper is to report our experience on the treatment of scleroderma ulcers with PRP and to provide a comprehensive overview of the available literature on this topic. Therefore, we present a case series of ten subjects treated with PRP gel for SS-related ulcers at our center. We also report the results of systematic literature revision of the available publications focusing on the use of PRP in the setting of SS ulcers.

Materials and Methods

Case series

Ten patients affected by SS-related ulcers were selected at our center (Dermatology Unit, Reggio Emilia Research Institute) according to the following criteria: i) age>18; ii) confirmed diagnosis of SS; iii) chronic skin ulcers lasting for at least 6 weeks; iv) resistance to conventional treatments, including prostanoids, phosphodiesterase 5 inhibitors, calcium channel blockers, antiplatelet agents and/or an 8-week course of optimal wound care. Homologous PRP was applied once a week until complete healing, for up to 8 applications. PRP gel was locally applied at the ulcer site and covered with paraffin gauze and secondary bandages. Photographic documentation of ulcers before and after PRP treatment was acquired, and the ulcer area was calculated. Each patient answered the VAS questionnaire to assess pain both at time 0 and at the end of treatment. Homologous PRP gel was prepared at the Transfusion Medicine Unit of the AUSL-IRCCS of Reggio Emilia according to the following protocol. PRP was obtained by healthy donors with platelet count above 180×109 plt/L. Platelet concentrate was collected through an automated apheresis procedure (MCS Collection System, Haemonetics Corp., Boston, MS, USA). The final unit of platelet concentrate had the following main characteristics: minimal residual plasma content, adequate preservative solution content to maintain pH>6.4 throughout the storage period; average final volume of 180 mL; platelet count of at least 2×10^{11} plt/unit. The units were irradiated at 35Gy and stored at 25°C until all the infectious screening results become available. PRP collected by apheresis was then processed with thrombin and calcium gluconate to obtain the gel preparation before administration.

Systematic literature review

A search was conducted on PubMed/Medline electronic database from inception to present. The detailed search strategy used the following terms: scleroderma [Title/Abstract]) AND PRP [Title/Abstract] OR platelet rich plasma [Title/Abstract] OR platelet gel [Title/Abstract] OR metabolite [Title/Abstract]. All the major journals were indexed. Only journal articles were taken into consideration, while books and book chapters were excluded. Articles without full text electronically available and/or English translation were also excluded. Only journal articles focused on scleroderma and PRP treatment were taken into account. Review articles were not included. The search was not restricted on human studies. The following data was collected for each paper: author, year, type of subject enrolled (human/animal), type of platelet-based product, administration (topical, injection), target of the treatment (sclerosis/ulcer), number of treated patients, site of treatment, controls, results.

Results

Ten patients were treated with PRP (8 females and 2 males), with a median age of 52.5 years. Ulcer size varied from 0.78 cm^2 to 28.26 cm^2. As for the anatomical sites involved, 5 were located on the fingers, 4 on the legs and 1 on the heel. Chronic skin ulcers were associated in 60% of cases with SS with limited skin involvement and in 40% with diffuse cutaneous SS. Raynaud's phenomenon was present in 90% of patients; telangiectasias, present in the face and/or hands, were also detected in the majority of cases (70%). Two patients presented with organ involvement. Clinical and demographic characteristics of the patients are summarized in Table 1. Baseline mean ulcer size was 7.57 cm^2 (±8.53) and mean VAS for pain was 6 (±1.2). Mean number of PRP applications was 4.7. The average ulcer size at the end of treatment was 1.04 cm^2 (±0.93), with a 78% reduction in ulcered area. All patients reported marked improvement in terms of pain score, with a mean VAS of 2±0.4 (SD) at the end of treatment. For further details on the characteristics of skin ulcers see Supplementary Table 1. Photographic documentation of two enrolled ulcers before and after PRP treatment is shown in Figure 1. With regards to systematic revision of the literature, the bibliographic research identified 92 publications, with 88 papers being considered after duplicate removal. No complete fulfillment of the other inclusion criteria was found in 78 papers. A total of 10 papers met all the research criteria and were therefore considered for the present work. The main characteristics of selected studies are reported in Table 2.

Table 1. Features of the 10 enrolled patients with systemic sclerosis and chronic ulcers.

	N. (%)
Sex	
Female	8 (80)
Age (median)	52.5
SS cutaneous subtypes	
Limited	6 (60)
Raynaud's phenomenon	9 (90)
Teleangiectasias	7 (70)
Organ involvement	2 (20)
Esophagopathy	1
Pulmonary fibrosis	1
Antibodies	
ANA	10 (100)
Anti-Scl-70 antibodies	3 (30)
Anti-ACA antibodies	8 (80)

SS, systemic sclerosis; ANA, antinuclear antibodies; Scl-70, anti-topoisomerase I Antibodies; ACA, anti-centromere antibodies.

Table 2. Characteristics of the main publications focusing on the use of platelet-rich plasma in the setting of scleroderma.

Author, year	Human *vs.* murine	Platelet-based product	Topical *vs.* injection	Ulcers *vs.* sclerosis	N. patients	Anatomical site	Control groups	Results
Wang, 2023	Murine	20% PRP + fat grafting	Injection	Sclerosis			Fat alone, PBS	Fibrosis (type III collagen) reduction, increase in VEGF, HGF, PDGF, CD31, IGF1R, PPARγ
Abellan Lopez, 2023	Human	PRP + micro-lipofilling	Injection	Sclerosis	13	Facial	Micro-lipofilling	Significant decrease in MHISS scale score at 6 months
Daumas, 2020	Murine	PRP alone and PRP + microfat	Injection	Sclerosis			Macrofat microfat, SVF, microfat+SVF	MF+ SVF and MF+PRP significant reduction (Coleman's procedure), of the dermal and the epidermal s clerosis; macrofat, SVF and PRP only corrected dermal sclerosis; only SVF alone or SVF+MF showed a significant increase of the vessel density
Pirrello, 2019	Human	PRP + hyaluronic acid	Injection	Sclerosis	10	Facial		Increase in mouth's opening, freedom of movement of the lips, and skin elasticity at 1-month and 2-y follow-up
Virzì, 2017	Human	PRP + SVF	Injection	Sclerosis	6	Facial		Improvement in buccal rhyme, skin elasticity and vascularization
Palumbo, 2017	Human	Heterologous PRP gel	Topical	Ulcers	1	Surgical wound (arteriovenous fistula)		Granulation tissue formation, wound healing
Shetty, 2016	Human	PRF	Topical	Ulcers	1	Acral (fingertips, toes,elbows)		Ulcer healing, pain reduction
Kanemaru, 2015	Human	PRP gel	Topical	Ulcers	2	Acral (fingertips, amputated knee)		Epithelization
Serratrice, 2014	Murine	PRP alone and PRP + microfat	Injection	Sclerosis			Macro-fat, MF, SVF, MF+SVF, MF+PRP	Fibrosis and vascular improvement; MF derived products more stable; SVF demonstrated better pro-angiogenic effects
Giuggioli, 2012	Human	PRP gel	Topical	Ulcers	12	Not specified		Improvement in wound size, pain VAS, HAQ

PRP, platelet-rich plasma; SVF, stromal vascular fraction; PBS, …; MF, …; MHISS, Mouth Handicap in Systemic Sclerosis; HAQ, health assessment questionnaire.

Globally, the retrieved publications included 45 patients treated with PRP-based therapeutic regimes.

The majority of these (n=29) were treated for microstomia and facial sclerosis.[10-12] PRP was generally combined with other therapeutic strategies (such as SVF, lipofilling or hyaluronic acid) and injected locally. All treated patients experienced significant improvement in terms of mouth's opening and skin elasticity.

With regards to the treatment of scleroderma-associated ulcers, most of the available literature is based on case reports.[13] The larger casuistry (n=12) on the use of topical PRP gel for the treatment of scleroderma-associated ulcers was published in 2012 by Giuggioli *et al*., who described PRP-mediated improvement in wound size and pain.[14]

Several authors proposed alternative types of platelet-containing preparations both in terms of source and processing, including protein rich fibrin (PRF) and heterologous PRP.[15,16]

Discussion and Conclusions

Chronic skin ulcers are today considered a major problem in the clinical setting, not only for the disease burden, but also for the impairment in patient quality of life and the healthcare costs. Inflammatory ulcers of SS are particularly disabling due either to the young age of patients and the poor response to treatment. Moreover, ulcers tend to occur in aesthetic areas such as fingers, therefore affecting patient professional and private life[5]. In addition, pain is almost constant in patients with SS-related ulcers.

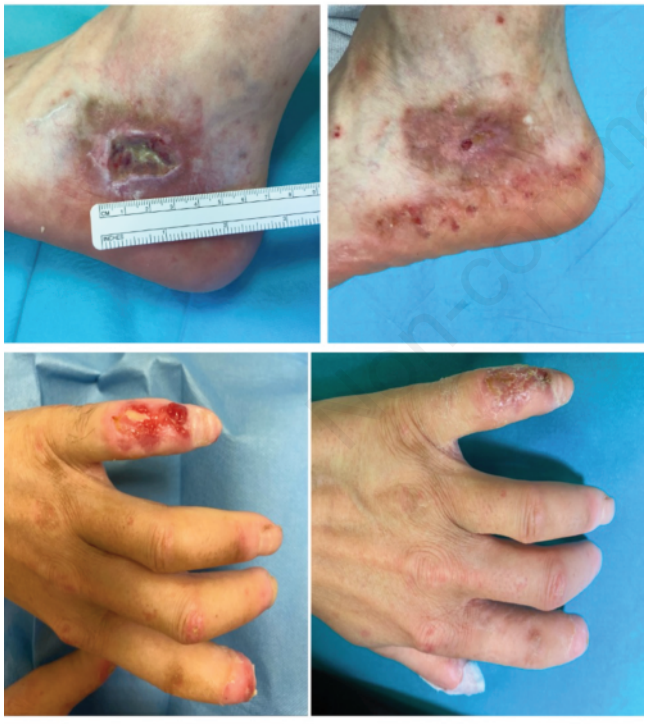

Figure 1. Clinical pictures of scleroderma-associated ulcers before (on the left) and after (right) treatment with platelet-rich plasma (PRP). Upper Panels: scleroderma skin ulcer of the V finger of left hand of a 45-year-old Caucasian female patient. Lower panels: Sclerodermic skin ulcer of the left lateral malleolar region of a 47-year-old Caucasian male patient. Left panels: skin ulcer before PRP treatment Right panels: after respectively 3 (top) or 6 (bottom) applications of homologous PRP once a week.

Notwithstanding, current guidelines on the classification and treatment of ulcers in the course of SS remain controversial.[6] Calcium antagonists, prostanoids, and endothelin receptor antagonists are routinely used for the treatment of SS-related; however, they results are still not satisfactory, especially for the healing of preexisting wounds. PRP promote and accelerate the wound healing process thanks to the release of cytokines, chemokines and growth factors. Over the last 10 years, PRP has been widely used for regenerative purposes in many dermatologic conditions, including alopecia areata, lichen sclerosus, acne scars, rejuvenation, vitiligo, and cutaneous ulcers.[4,7] In particular, the use of PRP has already been described as effective for in the treatment of vascular and diabetic ulcers of the lower limbs, ulcered lipoid necrobiosis and even SS ulcers.[8,9]

As suggested by the data retrieved through systematic literature revision, PRP-based strategies seem to be particularly effective in the setting of SS, especially in the treatment of acral sclerosis and/or SS-related ulcers. However, current evidence is mostly limited to case reports and case series and randomized clinical trial are lacking. To date, three comparative studies were conducted on murine models of scleroderma to compare the effectiveness of PRP with other regenerative strategies (Table 2). Collectively, the authors bring to evidence the effectiveness of PRP, especially when co-administered with adipose sources such as micro-fat.[17-19] However, SVF (stromal vascular fraction) seemed to bring better results in terms of vascularization when compared to PRP-based strategies.[18,19]

Several authors already hypothesized that platelet hyperactivation could contribute to the pathogenesis of scleroderma-related vasculopathy,[20] therefore suggesting possible limitations of autologous PRP treatment in this subset of patients. Similar evidence is also available for other regenerative strategies, since aberrant mesenchymal stromal cells have been described in patients affected by systemic sclerosis.[12]

Not only the use of homologous PRP potentially overcomes the intrinsic limitations of autologous regenerative sources in the setting of a systemic disorder, but also seems to have higher platelet and growth factors content, high degree of purity and a high degree of standardization.

Taken together, our results confirm these notions showing that PRP induces a reduction in ulcer size of 78% in an average of 5 weeks and promotes an improvement on pain associated with SS-related ulcers. However, despite the promising results achieved with PRP in the treatment of SS-related ulcers, further studies are needed to confirm our data and validate the use of PRP in the clinical scenario.

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Supplementary material

Table S1. Scleroderma skin ulcers features (size and site), before treatment and after the end of treatment. Number of weeks necessary to healing process.