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Regenerative therapies in lichen sclerosus genitalis patients and possible efficacy in preventing squamous cell carcinoma development: a long-term follow-up pilot study

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Key words: genital lichen sclerosus; squamous cell carcinoma; adipose-derived stem cells; platelet-rich plasma (PRP).

Authors' contributions: MT, designed the research study; MT, TP, AB, performed the surgery; MT, LA, performed PRP treatments; AL, LA performed the follow-up; LA, MDP, CC, collected the data; BB, analyzed the data, performed the statistical analysis for this study drafting the article; EM, supervised the activities; SDF, EM, performed critical revisions of the manuscript. All authors contributed to data interpretation and approved the final version of the manuscript.

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Informed consent: the Declaration of Helsinki Principles was followed, and patients gave written informed consent.

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Abstract

Lichen sclerosus (LS) is a chronic scleroatrophic dermatosis of unknown etiology that usually affects the anogenital area and occasionally the extragenital sites, which has no definitive cure. LS patients are at higher risk of developing squamous cell carcinoma (SCC) in their lifetime compared to the general population. Through a retrospective study, we evaluated the impact of regenerative medicine-based therapies on SCC onset in the context of genital LS.

LS patients treated in our institute from March 2013 to December 2022 were reviewed. A total of 319 patients, including 34 treated with adipose-derived stem cells (ADSCs) graft, 31 treated with ADSCs graft and PRP, and 254 treated with platelet-rich plasma (PRP) were identified. In parallel, data extracted from the histologic institutional database searching for SCC in the anogenital area were matched to surgical records.

None of the 319 LS patients developed skin SCC in the anogenital area. Our data suggest that cellular and acellular therapies achieving therapeutic control prevent continuous tissue remodeling and its evolution and, therefore, neoplastic degeneration.

Regenerative approaches are considered a valid strategy for treating LS patients symptomatic despite prolonged first-line medical treatment. Studying genital carcinogenesis of LS cases, we reported for the first time a protective role of PRP, ADSCs, and combined therapies. Thus, in terms of cancer prevention, we propose that regenerative therapies ameliorating disease control of non-responders to conventional therapy represent an important innovative tool.

Introduction

Several experimental and clinical shreds of evidence documented the possibility of potentiating intrinsic restorative and defense capacity through the regenerative medicine approach. Acellular therapies, which include the usage of stem cell-derived extracellular matrix, purified secreted vesicles, the entire secretome, platelet-rich plasma (PRP), and natural or synthetic polymers, aim to enhance tissue spontaneous restorative capacity. Cellular-based therapies involving mesenchymal stem cells (MSCs) graft-based significantly advanced the regenerative medicine field since this special type of cell is a non-specialized cell with the ability to self-renewal and differentiate into various cell types.[1] Thus, autologous stem cells sourced in disease or injury uninvolved tissue are useful to treat pathological conditions involving stem cell exhaustion as well as to accelerate natural tissue restoration. Among the several sources of MSCs, adipose-derived tissue stem cells (ADSCs) have received major interest due to the extremely high number of staminal elements, regenerative capacities, easy access, and the immune-privileged setting.[2] However, it is important to take into consideration that a large proportion of the desired effects of stem cell therapy may be attributable to adipose tissue-derived secretome containing many growth factors, lipids, and extracellular matrix components implicated in cell proliferation and tissue remodeling.[3] Moreover, since MSCs are immune-privileged cells that secrete a wide panel of cytokines, their ability to alter the host immune environment represents a promising treatment for inflammatory-associated diseases and autoimmune diseases.[4] Accordingly, very recently, the infusion of MSCs has been used to alleviate the non-protective cytokines storm of severe acute respiratory syndrome (SARS-CoV-2) patients.[5]

Currently, regenerative approaches are considered a valid strategy for treating Lichen sclerosus (LS) patients symptomatic despite prolonged medical treatment.[6] LS is a chronic relapsing, inflammatory mucocutaneous skin disorder usually involving the anogenital ivory-white patches, ulcerations, ecchymosis, atrophy with sclerosis, subversion of normal anogenital architecture including fusion or loss of the labia minora, narrowing of the vaginal introitus and burying of the clitoris culminating in urinary and sexual dysfunction.[7] Genital dysplasia is frequent, and there is also an increased risk of squamous carcinoma of the penis and vulva.[8,9,10] The risk of anogenital SCC associated to LS corresponds to 2% for men.[9] Large epidemiological studies evidenced that women affected with vulvar LS have a lifetime risk of developing squamous cell carcinoma comprised between 2 and 7%, while up to 65% of vulvar carcinomas arise in a background of genital LS.[11,12] Additional evidence showed that the local recurrence of a vulval SCC is greater in those with LS.[12] Some studies reported that SCC development is predominantly associated with female genital LS[13] whereas others reported no gender differences.[14] The association with SCC seems to be very specific since melanoma, basal

cell carcinoma (BCC), and Merkel cell carcinoma are all sporadically reported in male and female patients with LS. Differently, SCC is not associated with extragenital LS.

Currently, treatment of LS is mainly initiated to relieve symptoms of pruritis and pain, to reduce the progression of skin alterations, and eventually decrease the risk of cancer. Accepted first-line treatment of LS in the active phase consists of the daily local application of potent corticosteroids, mainly clobetasol propionate, whereas topical preparation of calcineurin inhibitors represents second-line treatment.[15] However, topical steroid therapy is not well-tolerated and successful in all LS patients. In general, adherence to prolonged topical therapy for cutaneous conditions is low.[16] Frequently, patients discontinue therapy for lack of rapid efficacy, resistance over time, or because of side effects (bacterial and fungal infection, thinning of the skin, dermal atrophy, dryness, and telangiectasia, acne, and mild depigmentation).[17] Moreover, a small percentage of LS patients are resistant to topical steroid treatment. However, in part, the lack of a definitive cure for LS reflects the fact that the exact etiopathogenesis remains unknown. Immunological dysreactivity, chronic inflammation, and pro-fibrotic fibroblast activation in a contest of susceptible genetic background are the major pathogenic mechanisms.[18]

For LS patients not responding to conventional pharmacological therapy, autologous ADSCs transplantation and combination of ADSCs to PRP demonstrated clinical improvement in most of the symptoms.[6,19] The biological rationale of PRP mixed with adipose tissue is based on the idea that PRP, being rich in several growth factors and cytokines, may contribute to fat graft survival.[20,21] Moreover, PRP modulates the immune system and extracellular synthesis, two altered conditions in LS. Accordingly, the injection of PRP alone also demonstrated significant clinical improvement in both male and female patients.[22] In this study, we analyzed the institutional patient database to evaluate the effects of regenerative therapeutic approaches (ADSCs, ADSCs combined with PRP therapy, or PRP alone) on the risk of genital LS progressing to SSC.

Materials and Methods

Patients' description

The research was approved by the Institutional Ethic Commitment. The study was performed in accordance with the Declaration of Helsinki, and all patients signed informed consent. This retrospective study covered a 9-year period (2013-2022) in a single hospital. 319 LS patients treated from March 2013 to December 2022 were identified through retrospective electronic medical record review: (a) 34 patients treated with ADSCs graft, (b) 31 patients treated with ADSCs graft plus PRP, and (c) 254 patients treated with PRP. These groups included patients still presenting symptoms due to poor corticosteroid efficacy, low compliance to therapy, or the relapsing nature of LS, causing the

progress onto a severe late stage. All patients discontinued the use of topical steroids one month before and during the regenerative treatment period. Detailed methods for ADSCs graft and PRP injection were previously described.[20-22] In brief, patients underwent PRP infiltration every 15 days, 3 times. Sometimes, one or more additional treatments were repeated and separated at least one year from the first infiltration. For ADSC-based graft, the patient received two or three surgical procedures in a day-surgery regimen in general anesthesia, distanced by a four-month period. Adipose tissue was obtained from the abdomen area. Patient follow-ups ranged from 1 to 9 years. However, considering 5 years as a minimum period for cancer surveillance, a subset of patients presenting this characteristic was analyzed separately. The overall patient population included 196 females and 123 males, with a mean age of 57,5±13 years (22-87 years). Anogenital SCC patients were extracted from the institutional database considering the period 2013-2023.

Statistical analysis

Descriptive statistics were used to describe the patients' characteristics. Quantitative data were reported as mean±standard deviation (SD). Student *t-test* was used to assess statistical significance with thresholds of *$p \leq 0.05$ and **$p \leq 0.01$.

Results

The study included 319 consecutive cases of histologically proven penile and vulvar LS mean age of 57,5±13 years; range 22-87 years) treated with regenerative medicine protocols in the Department of Plastic and Reconstructive Surgery of our institute. Gender distribution encompassed 196 females (mean age 58,8±12) and 123 males (mean age 53,8±14). In line with previous data reporting a significantly lower median onset age in males compared to females,[21] in this study, the gender-related age difference was statistically significant ($p=0.000062$) (Figure1).

Here, patients were divided into three groups: Group 1 (n=254) being injected with PRP, Group 2 (n=34) receiving an autologous ADSCs graft, and Group 3 (n=31) receiving both treatments (Figure 2). Among subjects included in Group 3, eighteen patients were injected with PRP and ADSCs in the same surgical event, of those, nine received additional PRP treatment during the follow-up; four were enrolled for PRP injection and then received ADSCs graft; ten underwent ADSCs graft and then received PRP during the follow-up. Short time (3 months) and longer (12 months) clinical follow-up confirmed previous data[6,22] concerning the effectiveness of treatments consisting in symptoms relief (itching, burning sensation, pain, and dyspareunia) and in the improvement of subjective findings (sexuality and the QoL of patients) (data not shown).

The median follow-up time was 4 years (mean 3,9±2,4 years; range 1-10 years), with the PRP group having shortened post-treatment observation period (mean 3,3±1,8 years; range 1-9 years) than

ADSCs (mean 5,8±3,1 years range 1-10 years) and ADSCs plus PRP (mean 6,9±2,3 years; range 1-10 years). Patients receiving PRP and ADSCs in the same surgical event (n=18) have longer clinical follow-up (8,5±0,55 years; range 7-9 years) since this specific procedure is not still used by our institute. A detail of follow-up period distribution among different treatment regimens is reported in Figure 3. Further selection for a minimum follow-up period of 5 years (median 7 years) evidenced 65 patients of Group 1, 23 patients of Group 2, and 25 LS patients of Group 3. Clinical observation showed that none of 319 LS patients developed an SCC or other type of skin cancer in the genital area (113 subjects with at least 5 years of follow-up). By contrast, the analysis of data extracted from the histologic institutional database confirmed the frequent occurrence of SCC in the genital area of anogenital LS patients since 18,5% of all anogenital SCC diagnosticated between 2013 and 2023 presented genital LS. No difference in age or gender distribution was observed when comparing the groups of SCC without LS background and SCC with LS background (Table 1). However, none of the patients with SCC and diagnosis of LS belonged to the group of patients treated with regenerative medicine therapies. The efficacy of regenerative treatments in SCC prevention is also indirectly reflected by the low percentage of anogenital SCC-LS (18,5%) among the entire anogenital SCC diagnosed in our institute. In fact, in the literature, the percentage of SCC occurring in LS background has been reported in the range of 31%-86%.[11,13]

Discussion and Conclusions

LS is a rare disease with a great impact on the well-being and quality of life of affected subjects. LS causes anxiety and depression due to the diminished ability to perform daily activities of living and sexual dysfunction. Nevertheless, due to under-reported symptoms by patients and the overlapping features with other dermatoses, early diagnosis and treatment of LS are difficult. The delay of the initial diagnosis of LS impacts symptoms and the prognosis, including the probability of progression to SCC. We observed a significantly lower median age for disease onset comparing gender differences. However, we cannot exclude that dissimilarity in clinical presentation and subjective perception among genders influence the timing of patients arriving at dermatology rather than the real disease onset. Accordingly, using a two-stage classification, previous studies reported that more than 67% of female subjects arrive at the diagnosis at a late stage, whereas only 46% of the males present late-stage characteristics at the first visit time.[22,23] Early intervention with topical corticosteroids may prevent both scarring and tumor evolution in males and females.[24] However, compliance with therapy also plays a relevant role in SCC onset. Women compliant with topical corticosteroid treatment demonstrate lower rates of vulvar SCC compared to women who were inconsistent with this treatment.[25] Some patients prematurely discontinue therapy for lack of prompt efficacy or because of

side effects. On the other hand, fears regarding long-term corticosteroid application undermine patient compliance and motivation. Thus, strategies recommended to minimize exposure to corticosteroids are needed for chronic skin diseases such as LS. Collectively, these studies suggest that considering the potential evolution towards cancer, LS needs to be treated, even when asymptomatic. Particularly, subclinical persistent inflammation engaging reactive oxygen species (ROS)-dependent tissue sclerosis and scarring might facilitate atypical hyperproliferative processes.[26] Due to the complicated pathogenesis, there is no definitive treatment strategy for LS patients. Ultrapotent topical corticosteroids' effectiveness lies in their anti-inflammatory effect via interaction with the intracellular glucocorticoid receptor and the immunosuppressive action, but clinical evidence of reduced dermal fibrosis[27] lacks a biological explanation. Other possible therapies sporadically used for LS patients, such as UV-A1, micro-ablative fractional radiofrequency, and topical retinoids, counteract the pro-fibrotic process, restoring normal collagen synthesis and metabolism.[28,29] Similarly, even if the loss of oxidative equilibrium is considered secondary to inflammation, direct targeting oxidative stress by systemic or topic supplementation with vitamin E and other antioxidants is retained as a valid adjuvant option to prevent disease progression and transformation into carcinoma.[30]

A wide repertoire of experimental and clinical studies illustrated that regenerative therapies act on most of the LS pathogenic mechanisms. PRP is a blood product enriched in growth factors and cytokines, which promotes tissue regeneration, angiogenesis, and immune modulation. Clinical studies demonstrated the efficacy of stem cell-enriched fat grafting in reducing fibrosis, pain, burning, and dyspareunia and restoring anatomical and functional in both male and female LS patients.[31] More, the combination of PRP and ADSCs seem to offer a synergistic approach to address the complex pathophysiology of LS, particularly in the early stages.[6] ADSCs' regenerative property relies not only on their cell replacement capacity but also on the secretion of trophic factors and modulation of the local immune response. Laboratory-based biological characterization of grafted material clearly showed that in addition to pluripotent cells, it contains direct ROS scavenger activity, stimulators of cell antioxidant endogenous capacity, immune-regulatory factors implicated in $CD8^+$ T cells proliferation and skin homing, molecules involved in extracellular matrix remodeling[2,32] explaining clinical shreds of evidence. Yet, questions regarding the oncological safety of therapeutic stem cells have been raised since many components required for successful regenerative therapy, such as re-vascularization, immunosuppression, and cellular mobilization, are also critical for tumor onset and relapse. *In vivo* studies documented divergent results showing a possible pro-carcinogenic risk in autologous adipose tissue-derived therapies,[33] as well as no increased risk of tumor recurrence in patient populations receiving adipose tissue-based intervention.[34] However, our and other previous *in*

vitro studies documented that, in contrast to normal cells, the proliferation rate of cancer cells (including skin squamous carcinoma and melanoma cells) is not affected or, in some cases, negatively influenced by adipose tissue-derived stem cell secretome.[2,34] In line with these data, here we report that no one of the LS patients treated with ADSCs, PRP, or ADSCs/PRP combined therapy developed SCC or BCC in the anogenital area during a medium-term follow-up, suggesting a protective role of these treatment options. The explanation might reside in the optimal control of disease symptoms or in the intrinsic propensity of transplanted material to interrupt the chronic inflammatory state typical of the dermal and epidermal skin of affected subjects and in the marked capacity to re-equilibrate the oxidative equilibrium since oxidative stress is deeply implicated in the carcinogenic process in LS.[35] In conclusion, data regarding the usage of regenerative therapies for LS patients confirm the safety and efficacy of these treatments encouraging further evaluation for cancer prevention. There is no doubt that disease control, particularly attenuation of the inflammatory cascade, acts to prevent the onset of genital SCC for patients with genital LS. However, the clinical data presented in this work suggest that regenerative medicine treatments, both surgical (ADSCs and ADSCs combined with PRP graft) and simple intradermal injection of PRP, have a strong impact on the restoration of physiological tissue balance and consequently on neoplastic evolution. The efficacy of regenerative treatments in SCC prevention is also indirectly reflected by the low percentage of anogenital SCC associated with LS diagnosed (18,5%) considering the total number of SCC (*e.g.,* LS-associated and not associated) since, in our institute, regenerative medicine-based therapies are routinely proposed at eligible LS patients. In fact, data in the literature described the percentage of SCC-LS over the total number of SCC, ranging from 31% to 86%.[11,13] Beyond the biological mechanisms underlying this observation, it is possible that this therapeutic option is intrinsically more effective than delegating long-term home management by the patient. In terms of cancer prevention, this leads to a reflection on the expansion of the offer of regenerative therapies not only to patients who do not respond to conventional therapies.

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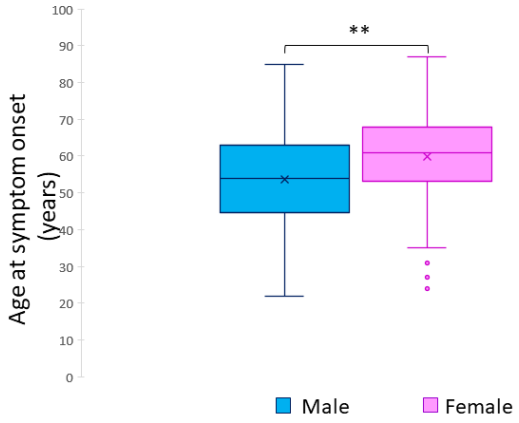

Figure 1. Plot of the difference in age. Age at the disease diagnosis was significantly lower in men compared to females (p=0.000062).

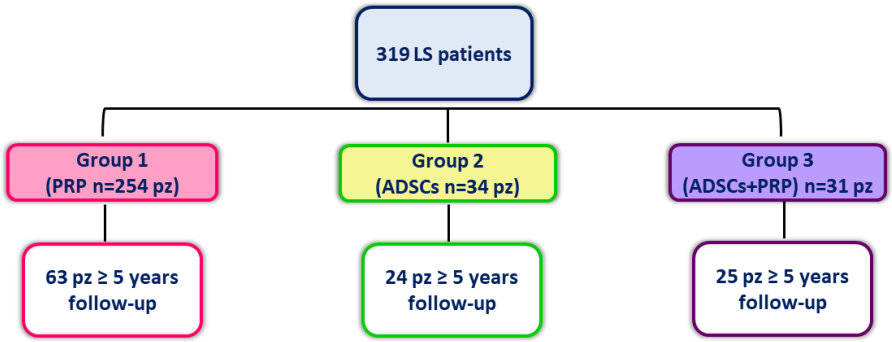

Figure 2. Graphical representation of patients' distribution according to the regenerative therapy used. The number of subjects with a minimal follow-up of 5 years is indicated in the lower boxes.

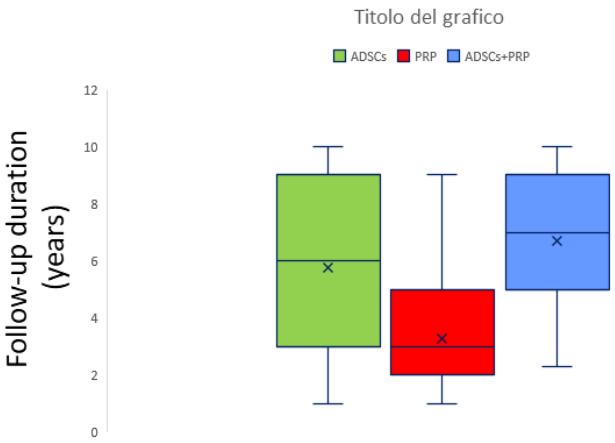

Figure 3. Plot of follow-up duration according to the type of regenerative therapy used.

Table 1	Age (mean±SD)	Age (range)	Male	Female	Number	%
SCC	65,6±14	29-93	94	54	148	(81,3%)
SCC with LS	78,1±11	40-91	26	8	34	(18,7%)

Table 1. Anogenital SCC patients' characteristics. The table includes anogenital SCC diagnosed between 2013 and 2023.