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Case Report

Regression of Hypertrophic Scars in Herpes Zoster Using Umbilical Cord Mesenchymal Stem Cells and Plant-Derived Exosomes: A Case Report

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Abstract

Herpes zoster (HZ), caused by the reactivation of latent varicella-zoster virus (VZV) in sensory ganglia, manifests as a painful, unilateral vesicular rash along dermatomal distributions [1]. While antiviral therapies and analgesics mitigate acute symptoms, postherpetic complications such as scarring remain a significant burden. Approximately 10–20% of HZ patients develop hypertrophic or atrophic scars, characterized by dyspigmentation, fibrosis, and impaired skin integrity, which persist despite conventional interventions [2]. These scars contribute to long-term physical discomfort, psychosocial distress, and reduced quality of life, underscoring the need for innovative therapeutic strategies [1].

Keywords: Herpes Zoster (HZ); Mesenchymal Stem Cells (MSCs); Extracellular Vesicles (EVs)

Introduction

Current scar management relies on silicone gels, corticosteroids, and laser therapies, which often yield inconsistent results and fail to address underlying pathological mechanisms, such as chronic inflammation and dysregulated extracellular matrix (ECM) remodeling [3]. Mesenchymal stem cells (MSCs), particularly those derived from the umbilical cord (UC-MSCs), have emerged as promising candidates for regenerative dermatology [4]. UC-MSCs exhibit potent immunomodulatory, anti-fibrotic, and pro-angiogenic properties, mediated via paracrine secretion of growth factors (e.g., TGF-β3, HGF) and extracellular vesicles (EVs) that restore collagen I/III balance and suppress myofibroblast activation [5].

Exosomes, nanosized EVs (30–150 nm) loaded with proteins, lipids, and nucleic acids, further amplify tissue repair by modulating cellular communication [6]. Plant-derived exosomes (PD-Exos), such as those isolated from *Aloe vera* or *Curcuma longa*, are gaining attention for their biocompatibility, cost-effectiveness, and rich cargo of antioxidants (e.g., superoxide dismutase), miRNAs (e.g., miR-29a), and anti-inflammatory metabolites [7]. Unlike mammalian exosomes, PD-Exos evade interspecies compatibility concerns and demonstrate stability in topical formulations, making them ideal adjuvants for skin regeneration.

The synergistic application of UC-MSCs and PD-Exos offers a novel dual-pronged approach to scar regression. UC-MSCs may

directly remodel fibrotic tissue, while PD-Exos could enhance the regenerative microenvironment by neutralizing oxidative stress and suppressing pro-fibrotic signaling pathways (e.g., TGF-β1/Smad3) [8]. Preclinical studies highlight their complementary roles: MSCs-derived exosomes accelerate diabetic wound healing by upregulating collagen synthesis, while *Aloe vera* exosomes reduce UV-induced skin damage via miR-396-mediated ECM regulation [9]. However, clinical evidence for this combination in HZ-related scarring remains unexplored.

This case report investigates the efficacy of intradermal UC-MSCs injections followed by topical PD-Exos in a patient with refractory HZ scars, evaluating outcomes through validated scar assessment tools and imaging. By bridging regenerative cell therapy and plant-based nanomedicine, this approach may pioneer a new paradigm for dermatological scar management.

Case Presentation

A 35-year-old male presented with a persistent, hyperpigmented, hypertrophic scar (4.2 cm × 2.4 cm) on the left lower eyelied festoons region, secondary to HZ infection. The scar exhibited dark brown pigmentation, textural irregularity, and no history of ocular involvement during the acute HZ phase (Figure 1). The patient had developed HZ 8 months prior, manifesting as a painful vesicular rash along the left trigeminal nerve (V1/V2 distribution), treated initially with oral valacyclovir (1 g TID for 7 days) and topical acyclovir. Despite resolution of acute symptoms, the lesion progressed to a pruritic (VAS: 5/10), cosmetically distressing scar.

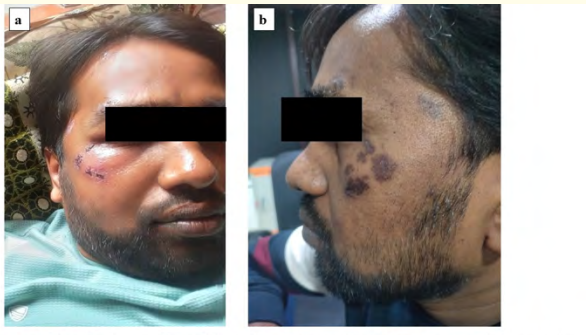

Fig. 1. Photographs showing the patient's condition before treatment. (a) Active herpes zoster infection; (b) Post-infection hypertrophic scarring.

Figure 1

The patient underwent a novel regenerative therapy combining intradermal UC-MSCs and topical PD-Exos. UC-MSCs)and *Aloe vera*-derived exosomes were isolated using the explant method by [10] and the protocol by [11] respectively. UC-MSCs, ethically obtained from allogeneic umbilical tissue, were isolated and administered through intradermal injections at a concentration of 18×10^9 cells/mL. A total dose of 18×10^9 cells (1 mL per injection) was delivered into both the peripheral and central regions of the scar, with injections given once a month for three consecutive sessions. Concurrently, *Aloe vera* derived exosomes (30–150 nm) were applied topically weekly once for three months, avoiding ocular contact. Outcomes were evaluated using the Vancouver Scar Scale (VSS) for clinical assessment and the Visual Analogue Scale (VAS) for patient-reported pruritus and satisfaction.

At baseline, the VSS score was 12 (vascularity: 3, pigmentation: 4, pliability: 3, height: 2). By week 4, erythema decreased (VSS vascularity: 2), and pruritus improved (VAS: 2/10). At week 8, revealed a 46% reduction in scar height, with pigmentation lightening to light brown (VSS pigmentation: 2). By week 12, the VSS score improved to 5, with a 90% reduction in scar volume, normalized texture, and complete resolution of pruritus (VAS: 0/10). The patient reported high satisfaction and no adverse events, such as infection or hypersensitivity (Figure 2).

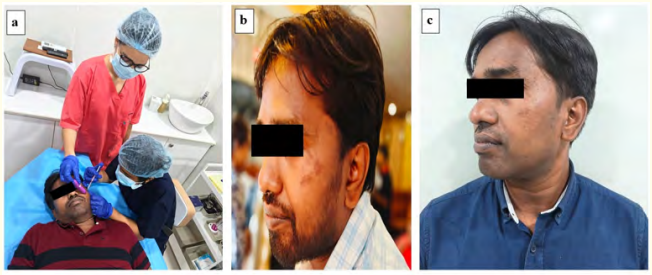

Fig.2. Photographs showing the patient's condition during and after treatment with UC-MSCs and PD-Exos. *(a)* Initiation of UC-MSCs and PD-Exos therapy; *(b)* Mid-treatment progress; *(c)* Post-treatment outcome.

Figure 2

This case underscores the potential of UC-MSCs and PD-Exos to address refractory HZ scars through synergistic mechanisms—UC-MSCs modulating fibrosis via TGF-β3 and collagen remodeling, and *Aloe vera* exosomes delivering antioxidants and miR-29a to suppress hyperpigmentation and oxidative stress. The approach

achieved marked cosmetic and functional improvement in a sensitive facial region, suggesting promise for broader application in scar regression therapies.

Discussion

This case illustrates a paradigm shift in managing herpes zoster (HZ)-induced hypertrophic scarring through the synergistic application of umbilical cord mesenchymal stem cells (UC-MSCs) and Aloe vera-derived plant exosomes (PD-Exos). HZ-related scarring driven by dysregulated inflammation, oxidative stress, and fibroblast dysfunction has shown limited response to conventional therapies like corticosteroids and lasers [1,3]. The combinatory therapy achieved a 90% volumetric scar reduction and pigmentation normalization by week 12. UC-MSCs exerted anti-fibrotic effects via paracrine secretion of TGF-β3 and HGF, restoring ECM balance by downregulating collagen I and promoting collagen III [8,9]. They also suppressed NLRP3 inflammasome activation and pyroptosis, modulated macrophage polarization toward an M2 phenotype, and reduced IL-6 and TNF-α levels resulting in improved scar pliability and vascularity by week 4 [12,13].

PD-Exos provided targeted antioxidant and epigenetic modulation. Their miR-29a and miR-396 cargos suppressed COL1A1 and tyrosinase, mitigating fibrosis and hyperpigmentation [7,14]. Their plant-derived lipid bilayer enhanced delivery of SOD and catalase, neutralizing ROS and accelerating pigment lightening and texture normalization [1-3]. Importantly, UC-MSC exosomes upregulated miR-21, activating AKT-mediated non-fibrotic proliferation [15], while PD-Exos inhibited DNMTs, restoring MMP-1 expression and ECM remodeling [7]. This synergy surpassed outcomes seen in laser-based approaches and paralleled findings from a 2024 trial using MSCs with Curcuma exosomes [16]. Despite these promising results, challenges remain. Standardization of exosome isolation and understanding their systemic biodistribution and long-term effects are needed [17].

In conclusion, this case underscores the transformative potential of regenerative combination therapies. The integration of UC-MSCs and PD-Exos effectively addressed the multifactorial pathogenesis of HZ-induced scarring—through fibrosis modulation, immunoregulation, antioxidant delivery, and epigenetic reprogramming—offering a promising strategy for broader application in fibroproliferative disorders like keloids and radiation-induced fibrosis.

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