CASE REPORT

Remediation of Mild, Acute Radiation Dermatitis Using a Stem Cell-Based Topical: A Real-World Case Report

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Abstract

Introduction: Wounds of the skin induced by irradiation involve a disruption of skin homeostasis and an increase in inflammation. Physiological renormalization treatment strategies using the molecules released from stem cells that restore proteostasis and regulate the immune system and reduce inflammation may be effective in treating skin conditions. Previous studies of severe radiation dermatitis found a significant reduction in symptoms using a combination product of the secretome from adipose mesenchymal stem cells and dermal fibroblasts, but mild radiation dermatitis has yet to be studied using this product.

Case presentation: This is a case report of radiation dermatitis in a patient with an uncommon cutaneous basosquamous cell carcinoma with perineural invasion that warranted radiation therapy. In this study we used S2RM technology, a proprietary combination of stem cell-released molecules from multiple types of skin stem cells, to renormalize homeostasis of the skin, including a renormalization of proteostasis to treat a mild form of radiation dermatitis induced by Intensity Modulated Radiation Therapy. Dramatic reductions in pain, redness, and inflammation, more rapid and complete wound healing, and an overall enhancement of the appearance of the skin were achieved in this patient.

Discussion: The current study demonstrates that as part of the palliative care strategies for cancer patients, the simple topical application of S2RM technology is a powerful means to renormalize homeostasis of the skin and remediate mild radiation dermatitis. The reduction of inflammation in the skin is important to reducing systemic inflammation and related comorbidities.

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Introduction

Radiotherapy is often associated with significant toxicities including radiation dermatitis. Severe toxicities of the skin may require interruptions of the radiotherapy series that can impair the treatment and prognoses of these patients.[1] The rate of grade ≥ 2 radiation dermatitis (RD) was reported to be about 90% even though the patients had received standard skin care.[2] Radiation-induced skin reactions (RISR) are often described as acute and chronic and classified on a scale of 1–4 using the Common Terminology Criteria for Adverse Events. Grade 1 changes include dry desquamation with generalized erythema. Grade 2 changes include brisk erythema or patchy moist desquamation. When the cumulative radiation dose reaches 40 Gy or higher, moist desquamation occurs at the folds of the skin. Grade 3 changes include extensive moist desquamation outside of the skin folds. Grade 4 changes include ulcers, bleeding, and skin necrosis. Acute RD occurs most frequently after irradiation of breast, pelvic area such as in the treatment of anal cancer and vulvar cancer, and head and neck malignancies, while a lower incidence rate has been found for deeper tumors such as lung cancers. The higher beam entry dose of the spread-out Bragg peak for protons versus photons[3] may underlie the increase in skin adverse effects found for proton treatments (PT) compared to photon radiation treatments,[4] although another study found little difference in skin toxicity when PT was compared to intensity modulated radiation therapy (IMRT).[5]

The mechanisms associated with RISRs include an inflammatory response, protein damage, and oxidative stress (OS). The inflammatory response and OS interact and promote each other.[6,7] After radiation-induced cell damage, cells die in various forms, especially mitotic

death, leading to inflammation and chronic OS. Proteostasis is disrupted by a number of mechanisms, including through damaging post-translational modifications of chaperokines including heat shock proteins.[8] In chronic phases, inflammation and OS can lead to changes in various cytokines, cell cycle changes, and DNA damage, sustaining the cascade and leading to late reactions. Fibrosis of the skin and soft tissue may progress from months to years after the treatment.[9] Chronic RISRs have a significant impact on the quality of life because of the irreversibility of the damage,[10] and the induction of systemic inflammation by skin inflammation.

Adipose mesenchymal stem cells (ADSCs) and their molecules, and dermal fibroblasts (FBs) and their molecules have been found to alleviate oxidative stress and resolve an inflammatory response,[11] and to release heat shock proteins that help to restore proteostasis in damaged tissue.[12] ADSC are preferred over bone marrow stem cells (BMSCs) for many reasons,[11,13] including that ADSC produce molecules that are significantly more effective at increasing the production of chaperokines than are the molecules released from BMSCs,[14] and induce macrophage polarization from a pro-inflammatory (M1) to a pro-repair (M2) phenotype.[15] ADSCs, fat tissue, and FBs have a demonstrated safety profile in oncology patients,[16,17] including a study by Toyserkani et al[18] showing that ADSCs and fat grafting for treating breast cancer-related lymphedema is safe and efficacious during a one year follow-up, and patient-reported outcomes improved significantly with time. Topical application of products just before radiotherapy is safe and not contraindicated, and does not impair focusing of the radiation to the target area.[19]

Previous studies found that severe cases of radiation dermatitis were significantly remediated by topical application of S2RM technology, the secretome from a combination of ADSCs and FBs.[20] However, mild radiation dermatitis[10] has not been previously treated with the S2RM technology. Even mild inflammation in human skin induces systemic inflammation[21] and may contribute to many inflammatory diseases through a number of mechanisms.[22]

Therefore, we used S2RM technology that combines the molecules from ADSCs and FBs, found to be safe in animal and human studies,[23] to treat radiation dermatitis in a patient undergoing radiotherapy for skin cancer. The aim of this case study was to determine whether, during real world conditions outside of a confined clinical trial,[24] standard skin care for mild radiation dermatitis could be improved with the addition of a topical product containing S2RM stem cell released molecules.

Stem Cell Released Molecules

A proprietary collection of stem cell lines derived from human skin were cultured using no penicillin/streptomycin under hypoxic conditions. When cultures reached confluence, they were passaged for a limited number of times before discarding. Total conditioned medium from the multiple cell types, containing a soluble fraction and an exosome fraction, was harvested at each passage and the passages combined into one batch for product development. The secretome from the two cell types, fibroblasts and adipose derived mesenchymal stem cells, contained both the exosome and the soluble fractions of the molecules released from the stem cells. The secretome uses a collection of proteins, microRNA, metabolites, and lipids, and some of its mechanisms of action are described in Maguire,[11] and its safety profile in Maguire and Friedman.[23] Parts of our stem cell technology used here are covered by US patents: 9545370; 9446075; 20140205563; 20130302273.

Case Presentation

The patient is a 67 year old male with a history of more than 30 nonmelanoma skin cancers in the past. He noted a left infraorbital lesion in October 2019 and a trial of topical imiquimod was initiated with no significant response which was unusual versus his past experience. Also unusual was that the lesion was tender, unlike any previous skin cancers. A punch biopsy of the 8 mm flat, brown lesion was performed by his dermatologist in January 2020 and was positive for basal cell carcinoma micronodular pattern with intradermal melanocytic nevus and squamous cell carcinoma with perineural invasion. CT scan of the neck on January 20, 2020 was negative for any evidence of disease.

He underwent resection of the residual tumor by a head and neck surgeon on February 18, 2020. Basosquamous cell carcinoma with extensive perineural invasion was noted in spite of negative margins being obtained, and the nerves involved were discontiguous with the primary ("skip lesions"). Adjuvant radiation therapy was advised due to high risk of locoregional recurrence.

The patient consulted a radiation oncologist on March 6, 2020 who proposed intensity modulated radiation therapy (IMRT) for 30 days of 6000 cGy. Pre-treatment MRI of the orbits revealed no visible lesions. Daily supplements included: Vitamin C 1000 mg, Zinc picolinate 25 mg, Copper citrate 1 mg, Green tea extract 75% EGCG 1000 mg, fruit blend 20% multianthocyanidins 300 mg, Tomato extract 10% lycopene 100 mg, Vitamin D 3 10 000 IU, Coriolus (Trametes) versicolor 1000 mg, Niacinamide 1000 mg, and compounded testosterone troche 65 mg sublingual.

Past history was notable for facial acne in his youth that was treated with superficial radiation. The patient has had extensive sun exposure as he was born and raised in Southern California and moved to Hawaii at age 32 where he has enjoyed an active outdoor lifestyle. Both parents were smokers and had lung cancer. Sister was diagnosed with melanoma on the lower extremity more than 10 years ago, managed with resection alone.

Intensity Modulated Radiation Therapy (IMRT) (with moist bolus to the skin) at a dose of 6000 cGy was delivered to left side of face from March 30, 2020 to May 11, 2020, five days per week (Monday through Friday for 6 weeks) for a total of 30 treatments.

Radiation-induced skin reaction

The patient complained of a 7-day history of mild to moderate radiation dermatitis despite using herbal moisturizing/recovery creams containing cannabidiol, turmeric, and Arum palestinum twice daily to the irradiated area from March 30 until April 19. S2RM treatment began on April 20, twenty days after radiotherapy began. The S2RM treatment was applied twice daily and the herbal creams were discontinued.

Pain

Prior to initiation of S2RM treatment (4/20/2020), the patient had mild burning pain in the irradiated area that he rated as 2/10 intensity. By the end of the first week of S2RM treatment, the pain had subsided to 0/10 and remained at that level except for a period of one week from 4/27/2020 – 5/4/2020 where the patient developed a shallow fissure in the skin fold distal to the left lateral canthus. This pain was of a stinging nature and rated 1/10. With a few applications of a sterile topical antibiotic ointment it quickly resolved. At no time was there desquamation.

Discussion

Acute radiation dermatitis (RD) is usually evident one to four weeks after the beginning of RT, and may last several weeks following the end of treatment.[25] The S2RM used in this study reduced the redness, pain, and irritation, and helped to more quickly repair the skin.

The skin's healing process and immune response to injury is complex. The mechanisms for the enhanced healing process induced by the S2RM likely are many fold. For example, S2RM may increase ceramide production in the keratinocytes of the epidermis, enhancing epidermal lamellar body formation and helping rebuild barrier function.[26] ADSCs also support re-epithelialization by providing guidance and paracrine instructions for maintenance of epidermal organization and homeostasis.[27] As part of the S2RM, exosomes secreted by human adipose mesenchymal stem cells promote scarless cutaneous repair by regulating extracellular matrix remodeling,[28] and rebuilding the dermal layer,[29] including human skin when applied

Figure 1. Patient undergoing IMRT for basosquamous cell carcinoma with extensive perineural invasion.

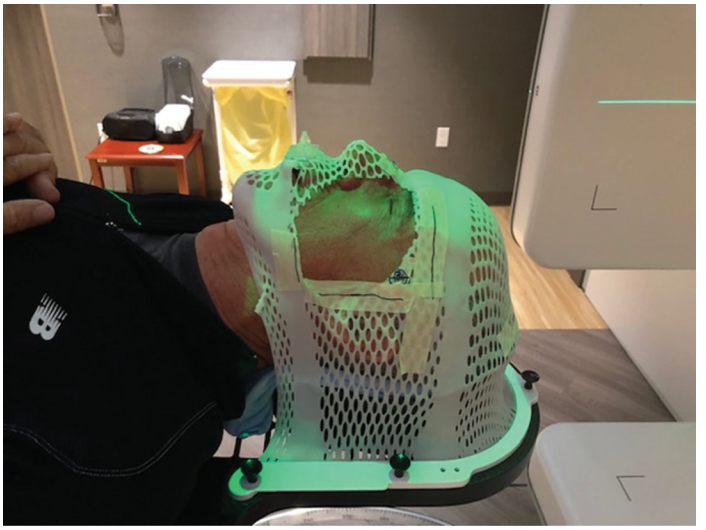

Figure 2. April 20, 2020

Figure 3. April 27, 2020

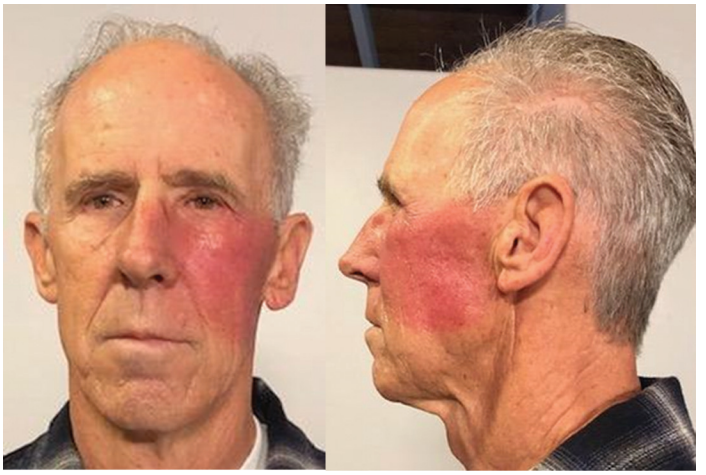

Figure 4. May 4, 2020

Figure 5. May 11, 2020

topically.[30] Also important to the radiation dermatitis sequlae is the reduction in skin inflammation and the reduction of fibrosis[31] that are induced by the molecules secreted by ADSCs.[32,33]

Strengths and Limitations to this approach and to this study

The limitations of this study are that we used an open label design with no controls. A comparison was made to herbal creams that are used in naturopathic medicine, and the results were significantly better once the naturopathic cream was switched to the S2RM product. If we ask the counterfactual question,[34] what would have happened had the patient not treated his skin with S2RM or had continued to use the naturopathic creams instead of the S2RM, then we understand that the condition of his skin and his pain would have not improved during the treatment. Thus, the positive results observed in this study were unlikely due to a placebo effect or simple healing. The current approach with a topical stem cell-based product to remediate acute pain and inflammation in irradiated skin will benefit from a follow-up study to determine whether the benefits are long term for chronic radiation dermatitis. Further, in ongoing case studies the benefit of the S2RM has been found to partially prevent radiation dermatitis, and to help repair the skin over a longer time course following radiation therapy.[20]

Table 1. Rating of skin condition and pain level beginning at week 0, when treatment began, and followed for 10 weeks. NC refers to three creams used in naturopathic practice containing cannabidiol, turmeric, and Arum palestinum, and S2RM is a topical product using the secretome from ADSCs and FBs. While the symptoms of radiation dermatitis were mild, the application of S2RM improved the symptoms quantitatively. The patient described his results: "My skin symptoms were always mild, but a 2 or 3-fold reduction in intensity was actually significant, from a subjective point of view."

Week	Treatment (NC or S2RM)	Skin Redness 0-10	Skin Irritation 0-10	Skin Pruritis 0-10	Pain Rating 0-10
0 3/30/20	NC	0	0	0	0
1 4/6/20	NC	1	0	0	0
2 4/13/20	NC	2	1	0	1
3 4/20/20	S2RM	3	2	1	2
4 4/27/20	S2RM	2	2	0	0
5 5/4/20	S2RM	1	2	0	1 fissure near eye
6 5/11/20 Final Rad Tx	S2RM	1	2	0	0
7 5/18/20	S2RM	1	1	0	0
8 5/25/20	S2RM	1	0	0	0
9 6/1/20	S2RM	0	0	0	0
10 6/8/20	S2RM	0	0	0	0

Conclusions

Our data, conforming to the results of many previous studies using ADSCs and FBs and their secretomes, suggest that the S2RM technology containing the secretome from multiple stem cell types, in a simple topical application, is an effective treatment for radiation dermatitis. It may also be helpful in the treatment of traumatic, autoimmune, and inflammatory conditions of the skin. Our data suggest that a physiological renormalization strategy[11] using topically applied stem cell released molecules is an important new clinical tool for palliative skin care in cancer patients undergoing radiation treatment. Controlled studies will need to be performed to corroborate these data found in our open-label case study.

Patient Perspective

The patient noted a brisk reduction in the erythema and pain in the irradiated area of his skin in the first week after starting the S2RM treatment. He was highly satisfied with the treatment and recommends it to others undergoing radiation therapy.

Patient Consent

Informed consent to publish this case report was provided by the patient.

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