Management of Late Radiation Tissue Injury Ulcers With Continuous Topical Oxygen Therapy Supports Wound Healing in Patients of Advanced Age Following Mohs Surgery: A Case Series

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ABSTRACT

Background. The long-term chronic effect of radiotherapy is commonly referred to as LRTI. Clinical complications such as skin atrophy, tissue fibrosis, endothelial damage, ulcer formation, and compromised wound healing are common sequela. Despite advances in medicine over the past decade, there remains a need for effective treatments for LRTI skin necrosis and ulcerations. **Materials and Methods.** This case series discusses cTOT in 3 patients of advanced age with LRTI wounds having undergone Mohs surgery. All wounds had been recalcitrant to multiple wound care treatments. All patients suffered with significant wound pain as well. **Results.** cTOT resulted in complete wound healing in all 3 patient cases. Additionally, all 3 patients reported a significant reduction in wound pain during the course of therapy. **Conclusions.** The positive outcomes exhibited in this case series suggest that cTOT is an effective treatment in the management of Mohs surgery patients with compromised wound healing due to radiation, advanced age, and comorbidities.

Keywords: chronic radiation wound, continuous topical oxygen therapy, late radiation tissue injury, Mohs surgery, pain reduction

Over the past decade, skin cancer incidence has been on the rise, increasing approximately 4% to 8% annually.[1] Due to the increasing commonality of skin cancers, health care providers frequently identify patients with these malignancies over the course of their clinical practice. Nonmelanoma cancers make up the majority of skin cancers (97%), with basal cell carcinomas accounting for 80% of these lesions and squamous cell carcinomas accounting for the remaining 20%.[1] In 2002, it was estimated that radiation therapy was used to treat over half of the approximately 1.2 million cases of cancer diagnosed in the United States annually.[2] Radiotherapy leverages high doses of radiation to destroy malignant cells, but often the healthy tissues within the field of radiation are also damaged. The complete extent of tissue damage may take weeks to months to develop.

The long-term chronic effect of radiotherapy is commonly referred to as LRTI. Clinical complications such as skin atrophy, tissue fibrosis, endothelial damage, ulcer formation, and compromised wound healing are common sequelae.[3] Despite advances in medicine over the past decade, there remains a need for effective treatments for LRTI-related skin necrosis and ulcerations. Customary therapies for LRTI include the use of topical retinoids, hydrocolloid dressings, tetrachlorodecaoxide dressings, topical thrombocytic growth factors, pentoxifylline, alpha-tocopherol, interferon-γ, and/or topical superoxide dismutase.[4,5]

Furthermore, radiation therapy is frequently used in the management of various skin cancers alone, or in combination with wide surgical excision or Mohs surgery. Mohs mi-

Abbreviations: CAMP, cellular and/or matrix product; cTOT, continuous topical oxygen therapy; LRTI, late radiation tissue injury.

crographic surgery is a well-established, specialized procedure used to remove skin cancers in which thin layers of skin are excised and examined under a microscope until a cancer-free tissue margin is achieved.[6] While Mohs surgery has the highest cure rate for cutaneous malignancies, postoperative wound healing can be protracted depending on tumor size, location, and depth, as well as patient age and comorbidities.[7] In fact, lower extremity defects after Mohs surgery that cannot be closed primarily often are a challenge to manage and result in a high number of complications.[7] Secondary intention healing after Mohs surgery can be further complicated by the damage to the epidermal and dermal tissue from LRTI. The high rate of postoperative skin failure in patients receiving Mohs surgery and radiotherapy may be a result of impaired microcirculation and tissue fibrosis leading to chronic, hard-to-heal, painful ulcerations.

The authors report a case series illustrating the successful management of chronic LRTI wounds with cTOT (NATROX®O_2; NATROX® Wound Care) (**Figure 1**).

MATERIALS AND METHODS

Three adults of advanced age received cTOT to manage their wounds after undergoing Mohs surgery. This method of cTOT consisted of a wearable device that generates pure oxygen from the environment and delivers it into the wounded tissue continuously at a rate of 11 mL per hour 24 hours a day.

For all patients, multiple advanced wound care therapies had been tried and failed. Due to the existence of LRTI and skin frailty in this patient cohort, these patients were not candidates for surgical intervention; thus, conservative management with cTOT was initiated. Patients were seen weekly, and cTOT was used through wound closure.

Organizational ethics board approval was obtained, Good Clinical Practice guidelines were followed, and informed consent was obtained for all patients.

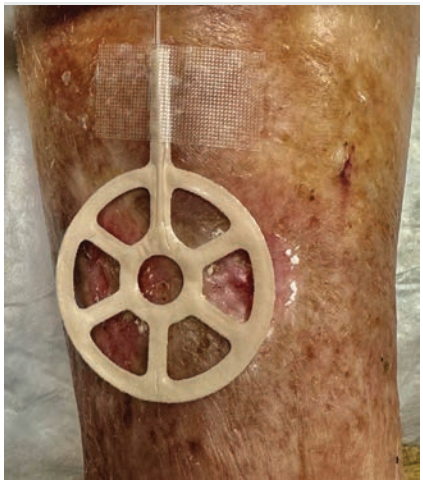

Figure 1. The proprietary continuous topical oxygen therapy device applied to a wound.

RESULTS

Three female patients aged 85, 91, and 93 years with a history of nonhealing lower extremity wounds due to LRTI were included in this case series. The mean postoperative wound duration was 13 months.

Case 1

An 85-year-old female presented with a nonhealing ulcer of the left lower extremity following Mohs surgery and radiation therapy to manage squamous cell carcinoma. The duration of the wound was 22 months. Past medical history included coronary artery disease, hyperthyroidism, cardiomyopathy, hyperlipidemia, venous insufficiency, and lymphedema. Previous treatment with surgical and ultrasonic debridement, various CAMPs, and compression bandaging had been performed without wound resolution.

At initial presentation the wound base appeared with moderate friable fibrotic tissue and measured 2.5 cm × 2.0 cm × 0.6 cm (**Figure 2A**). The patient's pain score at baseline was 5 on a 10-point numeric rating scale (0 = no pain, 10 = worst pain). The

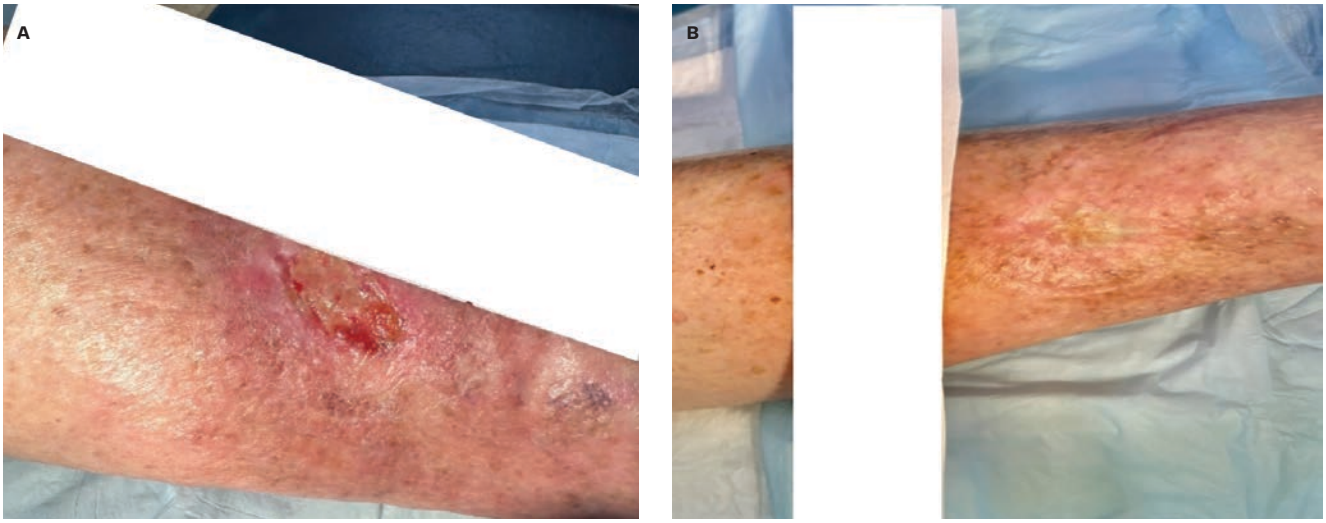

Figure 2. Case 1. (A) Nonhealing ulcer on the left lower extremity at baseline. (B) Complete epithelialization following 5 weeks of continuous topical oxygen therapy.

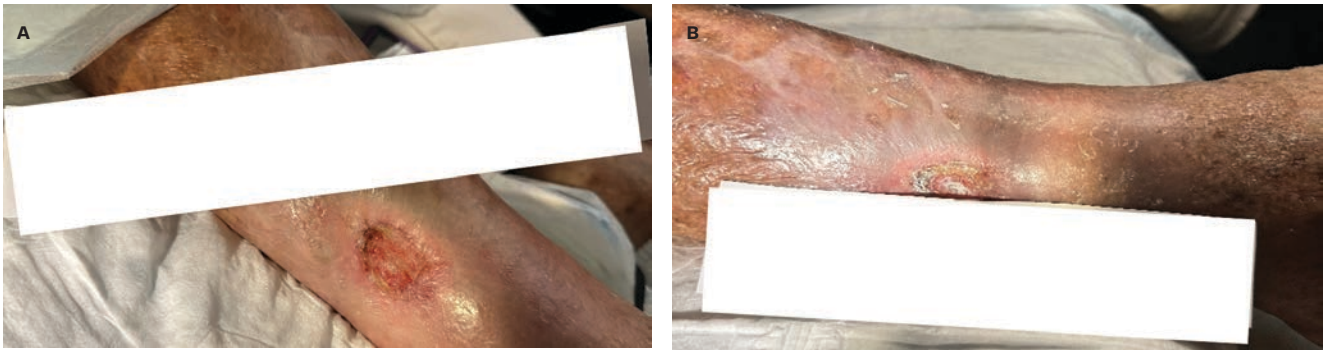

Figure 3. Case 2. (A) Nonhealing ulcer on the right lower extremity at baseline. (B) Complete epithelialization following 3 weeks of continuous topical oxygen therapy.

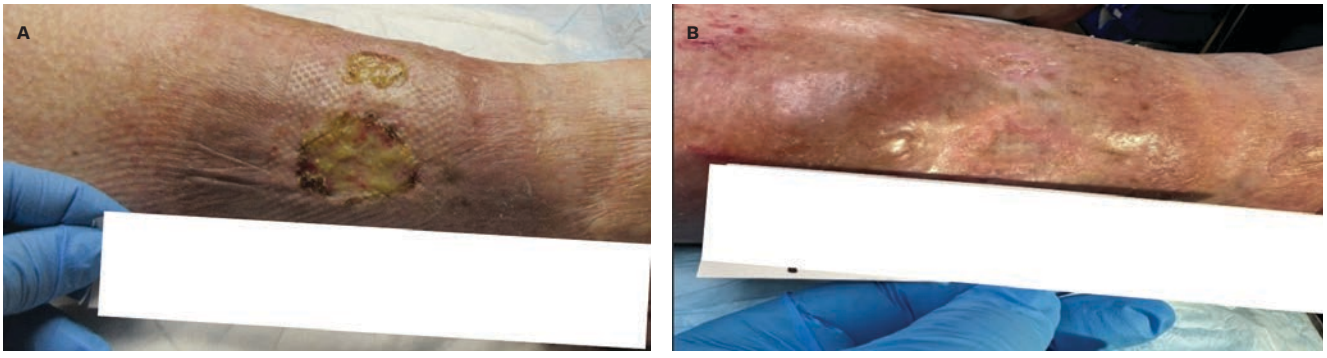

Figure 4. Case 3. (A) Nonhealing ulcer on the right lower extremity at baseline. (B) Complete epithelialization following 3 weeks of continuous topical oxygen therapy.

patient was treated with low-frequency ultrasonic debridement to prepare the wound bed, and the cTOT device was applied to the wound per manufacturer instructions and covered with a semipermeable dressing to maintain a moist wound environment.

The patient was seen twice weekly for dressing change, evaluation, and assessment. The oxygen delivery system of the cTOT device was replaced at each dressing change and covered with a semipermeable dressing. By week 1, the patient noted a pain score of 0. Complete epithelialization was achieved 5 weeks after cTOT was initiated (**Figure 2B**).

Case 2

A 93-year-old female presented with a nonhealing ulcer of the right lower extremity following Mohs surgery and radiation therapy to manage basal cell carcinoma. The wound had been present 11 months. Past medical history included hypothyroidism, peripheral arterial disease, and cardiomyopathy. Previous treatment with angioplasty, oral antibiotics, ultrasonic debridement, and various CAMPs had not resulted in wound resolution. The wound base appeared with adherent slough tissue and measured 3.4 cm × 2.2 cm × 0.5 cm at baseline (**Figure 3A**). The patient indicated a pain score of 10 on the 10-point numeric rating scale at baseline.

The patient was treated with low-frequency ultrasonic debridement, and cTOT was applied to the wound per manufacturer instructions and covered with a semipermeable dressing to maintain a moist wound environment. The patient was seen twice weekly for dressing change, evaluation, and assessment. The oxygen delivery system of the cTOT device was replaced at each dressing change and covered with a semipermeable dressing. By week 1, the patient reported a pain score of 3. Complete epithelialization was achieved 3 weeks after cTOT was initiated, as shown in **Figure 3B**.

Case 3

A 91-year-old female presented with a nonhealing ulcer of the right lower extremity following Mohs surgery and radiation therapy to manage squamous cell carcinoma. The wound duration was 8 months. Past medical history included cardiomyopathy, lower extremity cellulitis, lymphedema, hypertension, hyperlipidemia, obesity, and hypothyroidism. Previous treatments consisting of ultrasonic debridement, various CAMPs, and compression bandaging had not led to wound resolution. The wound base appeared with adherent slough tissue and measured 3.0 cm × 2.5 cm × 0.6 cm (**Figure 4A**). The patient reported a pain score of 5 on the 10-point numeric rating scale at baseline.

The patient was treated with low-frequency ultrasonic debridement, and cTOT was applied to the wound per manufacturer instructions and covered with a semipermeable dressing to maintain a moist wound environment. The patient was seen twice weekly for dressing change, evaluation, and assessment. The oxygen delivery system of the cTOT device was replaced at each dressing change and covered with a semipermeable dressing. By week 1, the patient reported a pain score of 0. Complete epithelialization was achieved 3 weeks after cTOT was initiated (**Figure 4B**).

DISCUSSION

Ionizing radiation causes damage to both malignant cells and healthy tissues alike. The pathogenesis of LRTI is progressive in nature. Indirect cell damage arises from the creation of toxic peroxides and free radicals resulting from the reaction of cellular and interstitial water with radiation.[8] Radiation also affects individual cells such as fibroblasts, causing downregulation in cellular signaling, resulting in altered collagen synthesis and disruption of tissue repair and regeneration.[9] Additionally, dermal fibrosis, fragmented elastin fibers, loss of rete ridges, and fibrotic changes in the microvasculature lead to soft tissue destruction and fibrosis of the skin.[9] As the skin ages, dermal collagen integrity decreases and skin fragility becomes more than just a cosmetic concern. The term *dermatoporosis* was coined to refer to the loss of protective mechanical function seen in aging skin.[10] Clinical manifestations of dermatoporosis begin to occur with increased incidence starting as early as age 60 years, but these manifestations are more acutely problematic in patients aged 70 to 90 years.[10]

The combination of dermatoporosis, surgical intervention, and radiation therapy in elderly patients can lead to serious sequelae such as nonhealing, chronic wounds.[10] Once the body's compensatory capacity is overwhelmed, the balance tips in favor of tissue destruction and ulceration. This process, which is often referred to as radionecrosis, can be extremely painful. It is believed that the underlying cause of LRTI is a limitation of oxygen delivery into the affected tissues.[11] A limitation of oxygen delivery due to LRTI to the affected tissues and the subsequent surgical intervention (Mohs procedure) resulted in delayed healing.[11]

Standardized treatment for chronic LRTI wounds, especially in the older population, is lacking. Conservative wound care consisting of cleaning, debridement, infection control, and nutritional support often does not support wound healing, as exemplified in the 3 cases in the current study in which wounds did not heal despite good standard of care.

Injured microcirculation and contraction of vessels in traumatized tissue limit oxygen distribution to a wound,[12] thereby reducing the wound's capacity to heal.[13,14] Oxygen plays an essential role in multiple wound healing processes, including oxidative killing of bacteria, cellular signaling and proliferation, collagen deposition, and angiogenesis.[15] It thereby stands to reason that reversal of hypoxic conditions in any nonhealing wound can support faster healing. By providing supplemental oxygen to wounded tissues, the essential functions of tissue repair and regeneration are supported and other barriers to healing such as chronic inflammation and infection can be minimized.

cTOT has been reported to support faster healing versus standard of care across multiple studies and wound types,[16-23] and this therapy provides the added advantage of wound pain reduction[24] and patient mobility during treatment.[15] The cTOT device used in the current case series proved to be an innovative, easy-to-use, lightweight appliance for delivering continuous oxygen directly to the wound bed through a long, thin, flexible tube connected directly to the cell phone–sized portable oxygen generator. The web-like wound interface of the oxygen delivery system permitted wound exudate to pass through to the secondary dressing, thereby maintaining a moist wound base without maceration. The cTOT device is portable; thus, oxygen delivery was maintained 24 hours a day, 7 days a week, allowing the patients to continue to perform activities of daily living uninterrupted. The treatment has been validated as low-risk, and it is easy to use in a wide range of care settings and for a variety of chronic wound types.[15,25]

The effect of cTOT on wound progression in nonhealing wounds observed in the current case series is in agreement with previously published data.[16-23] This series also highlights additional benefits in terms of marked wound pain reduction when using cTOT, which was previously reported by Jebril et al.[24] To the authors' knowledge, the current case series is the first to document healing in LRTI wounds with the use of cTOT.

LIMITATIONS

The current case series has limitations. The small sample size makes it difficult to draw sound conclusions about the effects of cTOT on LRTI wound management. However, this case series lends credence to the idea of using cTOT in the management of LRTI ulcers. Evidence-based therapies for this patient population are lacking, and additional research is needed. Further clinical trials with larger recruitment and carefully planned intervention and outcome measures would be ideal.

CONCLUSION

Given the mechanism of action of cTOT, the authors of the current series believe that reestablishment of adequate blood and oxygen to wounded tissues supported the rapid wound healing and pain relief observed in these 3 patients. The positive outcomes exhibited in this case series suggest that cTOT is an effective option in the treatment of patients who have undergone Mohs surgery and who have compromised wound healing due to radiation, advanced age, and comorbidities.

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