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Cutaneous Radiation Injuries: REAC/TS Clinical Experience

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Brief Report

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Abstract

The Radiation Emergency Assistance Center/Training Site (REAC/TS) is one of the US Department of Energy (DOE)/National Nuclear Security Administration (NNSA) Nuclear Emergency Response Team (NEST) assets and has been responding to radiological incidents since 1976. REAC/TS is in the Oak Ridge Institute for Science and Education (ORISE). A critical part of the REAC/TS mission is to provide emergency response, advice, and consultation on injuries and illnesses caused from ionizing radiation. Fortunately, radiation injuries are not frequent, but when they occur, they are more likely to be cutaneous radiation injuries (CRI) or internal contamination. In this paper, we will review selected cases from the REAC/TS experience in order to illustrate cutaneous patterns of injury and treatment options.

Materials and Methods

Selected cases from the REAC/TS experience are reviewed, illustrating patterns of injury and treatment options. The REAC/TS registry, under Institutional Review Board ORAU (79)-63, The US Radiation Accident Registry follow-up program, is the original source of the information included.

Several authors have previously reported the relatively high occurrences of CRI in the cohort of individuals with exposure scenarios, over the last few decades.[1-3] When reviewing 44 years of radiation incidents, a pattern was noted that when the whole-body dose was 6 Gy or more, significant CRI were present in approximately one-third of cases.[4]

At the core of cutaneous radiation injury is the impact of ionizing radiation on cellular DNA and, depending on the efficacy of innate repair mechanism, either the eventual recovery or cellular death. In this type of radiation injury, the most significant targets are epidermal stem cells or other subcutaneous organ/tissue stem cells (such as epithelial cells). DNA injury can occur via a direct energy transfer to the genetic material or indirectly from reactive oxygen species (ROS).[5]

The subsequent and repeated associated inflammatory response seen following radiation injury compounds the initial biologic insult and can lead to some of the unique late findings in cutaneous radiation injury such as telangiectasias, injury re-exacerbation, fibrosis, and atrophy. This response is brought on by neutrophils that will initiate the release of these inflammatory cytokines, mainly mediated by interleukin-1 (IL-1) and tumor necrosis factor alpha (TNFα). Vasoactive substances contribute to local vascular dilation while damage to the vascular endothelium results in increased capillary permeability and increased movement of intravascular contents into the surrounding third space. Local microhemorrhages can occur, which fuel pathologic platelet consumption and coagulopathy. Plasmin breaks up resulting fibrin clots and activates Factor XII, which in turn activates the (1) kinin system that activates Factor XII and forms bradykinin causing an increase in vascular permeability/vasodilation; (2) clotting cascade resulting in clotting and inflammation; (3) fibrinolysis lyses clots and activates Complement; and (4) Complement increases vascular permeability/vasodilation, thus a continuous feedback loop.[5,6]

The expression of Major Histocompatibility Complex II (MHC II) molecules (like dendritic cells) will happen with the recruitment of monocytes, neutrophils, other antigen presenting cells (APCs), macrophages, platelets, lymphocytes, and eosinophils. An excess of Transforming Growth Factor β-1 (TGFβ-1) may lead to radiofibrosis and may extend into vessels and deeper tissues. In advanced cases, subsequent infiltration of polymorphonuclear (PMN) leukocytes, and lymphocytes along with mast cells activation, degranulation, and release of TNFα, may occur, leading to perivascular edema, progressive cellular hypoxia, and, ultimately, cellular death. This will be covered in more depth in other articles in this special issue.

The evaluation of patients with potential cutaneous radiation injuries should start, as always, with a good patient history and physical exam to ascertain any acutely life-threatening physical

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Table 1. Grading of severity

Parameter	Grading/severity of damage			
	Mild–C1	Moderate–C2	Severe–C3	Serious or potentially fatal–C44
Erythema	Primary disappears quickly; secondary usually ~ weeks	< 10% TBSA	10–40% TBSA	≥ 40% TBSA
Ulceration/necrosis	No	No	Ulceration	Necrosis

Modification of METREPOL grading from Medical Management of Radiation Accidents: Management of the Acute Radiation Syndrome. Published by The British Institute of Radiology, 2001. ISBN 0-905749-46-4.[10]

Table 2. Clinical dose thresholds

Dose (Gy)	Sign	Timing
3	Epilation	Begins around days 14–17
6	Erythema Distinguish from thermal burn	Minutes to weeks, depending upon dose
10–15	Dry desquamation	2–3 weeks post-exposure, depending upon dose
15–20	Moist desquamation	2–3 weeks post-exposure, depending upon dose
> 25	Deep ulceration Radionecrosis	> 21 days

Modified NCRP Clinical Dose Threshold from NCRP 161, 2009.[11]

findings, existence of pre-injury morbidities, and other potential risk factors. Once the patient is determined to be clinically stable and at no acute risk to life, it is critical to attempt to understand the circumstances surrounding the suspected radiation exposure. If available, be knowledgeable of the isotopes or type of ionizing radiation, dosimetry (or dose reconstruction), the total time of exposure, and the distance of the patient from the suspected sources. The French have used this information to do Phantom modeling of the incident for dose mapping.[7] This information can provide important information and, when combined with the clinical presentation, may help guide treatment.

Imaging studies such as MRI, MRA, soft tissue ultrasound, thermography, and optical coherence tomography angiography have been shown to provide insights into the extent and depth of radiation trauma.[5] Depending on an individual patient's injury scenario, biodosimetry techniques such as gamma H2AX assay of hair follicles, DSB markers (53BP), protein signatures, and EPR of hard tissues may help better define the scope of the radiation damage.[8]

Grading scales have been developed to describe and categorize the severity of individual cutaneous radiation injuries. The NIH Common Terminology Criteria for Adverse Events (CTCAE) provides 5 grades ranging from light erythema (Grade 1) to ulceration/skin loss (Grade 4) and fatal injuries (Grade 5).[9] Another grading system based on clinical presentation and affected percentage of body surface area is the METREPOL Cutaneous System Grading scale, which provides a broad prediction of prognosis related to injury severity (Table 1).[10] In many cases, the clinical findings will often provide the most accurate estimation of the actual radiation dose received by the patient. A modification of the NCRP Clinical Dose Threshold table (Table 2) correlates the degree of injury to the skin and the time to presentation to a predicted ionizing radiation absorbed dose.[11]

It is tempting to view the treatment of cutaneous radiation injuries as being on a spectrum shared by thermal burn trauma. While there are many aspects of traditional burn trauma management that overlap with the treatment of radiation injury to the skin, the differing mechanisms of injury can drive a divergence in prescriptive medical care. While the two injury types both benefit from the debridement of non-viable tissue, radiation injuries will often take weeks, months, and possibly years to fully evolve the extent of non-recoverable skin and soft tissue. The long-lasting and late-appearing morbidities, such as radiation fibrosis, chronic wound pain, recurrence of tissue loss, and non-healing wounds, often occur well after initial wound healing is complete and are rarely seen in recovered thermal burn patients.

In severe (> 25 Gy) radiation exposures, the cutaneous injuries may become very complex, unpredictable, and recurring injuries. In these cases, both local soft tissue infection and opportunistic systemic infections can complicate and delay the healing of the affected soft tissue. Göttlober et al. reported findings showing evidence of cutaneous radiation wounds in 54 of the 134 Chernobyl ARS cases and that greater than 50% (16 of 28) of acute deaths following that tragedy were secondary to cutaneous radiation wounds and not hemopoietic failure.[12] This aligns closely with our review of 578 major radiation accident patients between 1944 and 1986 recorded in the REAC/TS registry that showed a 32% incidence of local radiation injuries in patients receiving a greater than 6 Gy ionizing radiation dose.[4]

Results

From the REAC/TS radiation injury registry, we will provide two descriptive cases of cutaneous radiation injury, the treatment options provided to them and subsequent clinical outcomes from their injuries before delving into our recommended treatments and interventions.

In the first case, a teletherapy engineer was changing out a 1400 Ci cobalt-60 source for a 6500 Ci source. He placed his hand in front of the shielding for a matter of seconds. Video reenactment estimated the dose to be 6–7 Gy. Conservative therapy resulted in apparent healing of the wound until the wound recurred approximately 1 year later after very minor trauma. The wound steadily worsened with conservative therapy and hyperbaric oxygen treatment, with subsequent osteoradionecrosis. This case ended in amputation. A thermography picture is included to show the degree of heat, represented by orange to red color, compared to the area of tissue breakdown (Figure 1).

REAC/TS initial conservative therapy recommendations for individuals with a suspected cutaneous radiation injury are designed to be easily initiated in an emergency room, occupational clinic, or other medical treatment facilities where a patient may first present for care. In all cases of radiation injury, the first clinical activity is always to address any acute, life-threatening injury or medical condition. From the first suspicion of localized radiation

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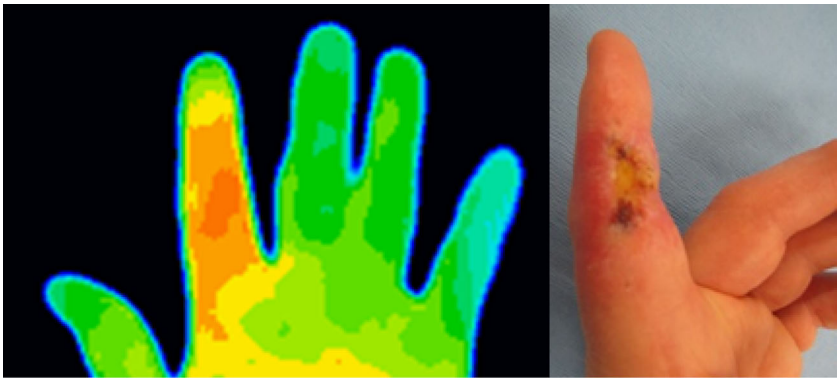

Figure 1. Thermography compared to wound, prior to amputation. From REAC/TS Registry.

injury, care should be taken to protect the area from further injury or insult as the tissue may look healthy now but will have already suffered serious harm to its mechanisms to heal. Care should be taken to avoid unnecessary use of strong adhesive tapes, obtaining blood samples, or starting IVs in the injured area. In many scenarios, personal and work restrictions will be necessary to protect the area involved even prior to the eventual physical expression of the wound in the form of blisters, ulcers, or progressive necrosis.

Initial treatments to afflicted skin to help mitigate the impact of the radiation injury are topical agents.[10] Topical antihistamines have traditionally provided some symptomatic relief to the sensation of burning and itching that are common at early presentation. But, in addition, there is evidence that antihistamine-mollification of mast cell excessive histamine release can not only reduce the above symptoms but also have been found to have anti-fibrotic properties in arthrofibrosis.[13] Silver-based topical anti-microbials can provide local protection from infectious challenges while emollient moisturizers are helpful in reducing breaks due to dry/callous skin. In some cases, topical (and, in some cases, subcutaneous or systemic) steroids can aid in muting the over expressive local immune response commonly seen in cutaneous radiation injury.[10]

In addition, a prescription of oral or topical alpha tocopherol and/or pentoxifylline can help reduce oxidative stress and inflammation and appear to be synergistic in effect.[14] Many providers will add scheduled non-steroidal anti-inflammatory medications (topical or oral) for reducing the local inflammatory response, as well as a non-opioid pain reliever. Especially in cases where concurrent soft tissue trauma exists in the radiation field, early consideration of antimicrobial prophylaxes and/or pre-sumptive treatment is indicated due to the potential of a compromised host immunity system.[6]

These generalized conservative therapeutic guidelines come principally from the collective experience of those treating the small number of cutaneous radiation injuries occurring in historical accidents, radiotherapy, burn management, and trans-lational research. There are some additional and newer techniques that are emerging as therapeutic options that we have added in as recommendations worth considering.[15]

The best clinical outcomes for cutaneous radiation injuries often require the input from a wide field of clinical consultants as part of a multi-disciplinary team. Nutrition specialists can ensure dietary intake and supplementation provide the patient with the appropriate building blocks to support wound healing. Depending on the site and extent of injury, surgical specialists from the disciplines of burn, trauma, plastics, hand, reconstructive, oncological, and general surgery may all have a role to play in the often-complex wound care in these cases. In some cases, dermatology may bring unique capabilities to the patient care team. In keeping with the long times that a patient will require to recover from these injuries, serial visits with rehabilitative medicine, wound care teams, and mental health specialists are essential for a healing process that may take months or years to complete.[15]

Local wound care options short of surgery are often sufficient initially but also serve as valuable conjuncts to more invasive surgical options. The choice of dressing can be traditional, but it is suggested that hydrocolloid/hydrogel-based wound covering be considered.[16,17] These dressings provide gentle adhesion, compared to adherence dressings, and water vapor transmission, that can augment wound infection control "and perform autolytic debridement of necrotic tissue by piggybacking on antibiotics or anti-inflammatory drugs during the inflammatory phase. In the proliferative phase, hydrogel dressings can promote vascular regeneration and fibroblast proliferation by releasing growth factors and degradation of bioactive materials. In addition, hydrogel dressings can also be used as tissue engineering scaffolds to piggyback on seeded cells or induce factors to promote tissue generation. The porous structure possessed by the hydrogel can absorb wound exudates, maintain the excellent permeability, and moist wound environment around the wound, and reduce the pain of patients to a certain extent."[18]

Certainly, surgical treatment is very important but with latent compromise to the viability of surrounding soft tissues, breakdown of initial wound closure and soft tissue coverage of wounds is not uncommon. Surgical debridement is the mainstay of radiation injuries, initially.[19,20] Unlike thermal burns that usually demonstrate clear margins of tissue viability and non-viability, radiation-induced skin injuries will often be deceiving intra-operatively as tissues that appear to have a robust blood supply will post-operatively fail to support adjacent grafts or become necrotic themselves. Following early debridement, improved success has been seen with coverage provided by skin substitutes such as biosynthetic/bioengineered epidermal or dermal skin grafts.[15,19]

Surgical options following debridement include partial and full thickness skin grafts, local advancement or rotational flaps of skin with underlying vascularized soft tissue, and vascularized free flaps transplanted from remote and minimally radiologically dosed areas of the body. As a last resort, limbs or digits deemed unsalvageable may be definitively treated with amputation. In these cases, great care must be employed in determining the level of

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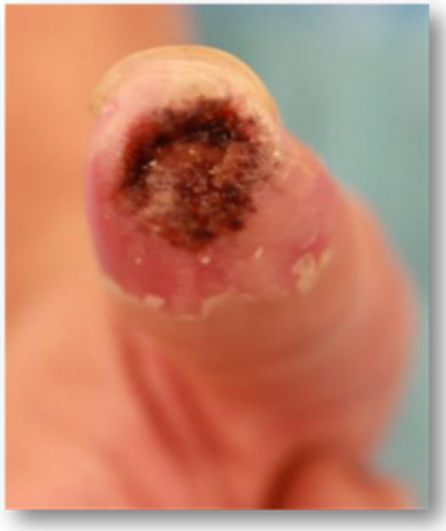

Figure 2. Wound recurrence, post incident day 650. Used with permission from HPJ, Iddins et al. HPJ 2016.[27]

amputation to ensure the remaining tissue at the stump site has not suffered sufficient radiologic injury to compromise effective healing of the stump closure wounds.[15]

Pre-operative and post-operative use of negative pressure wound therapy, hyperbaric oxygen therapy, and platelet antiaggregating agents have shown promise in reducing time to healing and wound complications.[21–23] It should be mentioned that in the United States insurance environment, approval for non-traditional therapies can be very difficult to obtain in a timely fashion and often requires the engagement of the treating physician and outside experts in these cases, in the experiences of the REAC/TS staff. For example, hyperbaric oxygen treatments, which is a therapeutic treatment frequently employed in dealing with chronic ulcers, have shown efficacy with soft tissue radiation injuries but in the REAC/TS experience require more treatments than usual for chronic wound or ulcer treatment. In our experience, it has often taken months of negotiations with insurance companies for approvals to successfully go through the appeals process.

One promising new treatment currently being studied in France and Japan is the potential role of Mesenchymal Stem Cell Therapy (MSCs) or Adipose-derived Stromal Vascular Fraction (stromal cells or SVF).[24–26] This treatment currently lacks FDA approval in the United States, but there are US-based research protocols currently looking at their use in thermal burn treatment that may allow humanitarian accommodations in particularly difficult cutaneous radiation injuries. In foreign trials, the injection of these stem cells has shown encouraging results in research protocols and has been commonly used in conjunction with other therapies such as growth factors, dermal constructs, wide local excision, skin grafts, flaps, and/or amputation.[24–26]

The second case was initially treated with conservative treatment with a clinical dose estimation and video reconstruction of dose estimation to be 20 Gy or less. With successive, worsening wound recurrences and lack of response to conservative therapies, approval through insurance for a "humanitarian treatment" of stromal vascular fraction injection was done.[27] This individual had an x-ray beam irradiate his thumb with a minor injury that healed; however, with the continued recurrences came increasing pain and paresthesias (Figure 2).[27] SVF injection was done with resolution of pain and paresthesias within 48 hours post-injection and without subsequent breakdown.[27]

Discussion

Cutaneous radiation injuries are not a common occurrence, though they may have a significant impact on a patient's quality of life when they do occur. There are recommendations for radiodermatitis; however, these injuries differ in that the dose was delivered in fractions and deliberately, not acutely and often without awareness of the individual. At or above a threshold absorbed dose, a large total body surface area, or partial-thickness or deeper involved areas, these may become very complex, non-healing or recurring wounds. The risk of morbidity from infectious complications may result in these conditions, as well. Even with isolated or localized wounds, there can be a great psychosocial impact on the patient.

There is a gap in evidence-based recommendations with current therapies derived from historical incidents; burn and radiodermatitis therapies; and translation from bench therapies. Some countries are using newer therapies, such as stem and stromal cells, from experience with various clinical trials. Though analogous clinical trials occur for thermal burns in the United States, there is no mechanism for the patient to be referred, outside of the clinical trial, for these often last resort/humanitarian therapies.

There is a gap in provider experience in treating these injuries due to infrequency of occurrences and often insufficient lack of communication among the various specialists treating the patients.

Conclusion

Research is ongoing for radiation cutaneous injuries. Innovative treatments such as stem/stromal cells with surgical procedures are widely covered in the literature and mentioned above. Advances with dressings and tissue constructs/substitutes are occurring. Progress has been made with the recent approval of a silver-based treatment device, Silverlon®, in the United States. Research in the United States is still primarily based in animal species, with the US Food and Drug Administration requiring research in two animal species before moving forward with the development of treatment agents or devices. There are so few clinical cases that this makes the possibilities of enrollment into clinical trials very challenging. These factors contribute to challenges in funding for this research. Success of animal model research is the most feasible answer, and progress is being made in many nations. Meanwhile, many of the individuals with these injuries need innovative, evidence-based therapies, as some of these outcomes may be of significant psychosocial impact. There is much to be done with bench and clinical research to further our knowledge and management of these injuries.

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