Cutaneous Radiation Syndrome: Review of Assessment and Management

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ABSTRACT

The cutaneous radiation syndrome (CRS) refers to a number of pathologies that may become a manifest after exposure of the skin to ionizing radiation. Signs and symptoms of the CRS appear within hours of exposure; however, the development of lesions can take days to years. The latent period for the manifestation of a specific pathology depends on the characteristics of the target cells responsible for the development of that lesion and the dose of radiation delivered to those target cells. The intensity and duration of the lesions are also dose dependent. Since the depth dose distribution of a radiation source depends on the radiation quality, the development of a specific lesion, its intensity and its duration is also expected to vary with radiation quality. The CRS may appear as an isolated lesion or as a number of lesions occurring simultaneously or over different time scales. In dealing with the cutaneous tissues, the concept of dose is meaningless unless it is associated with a reference depth dose distribution to indicate the level of injury to specific target cells. Large radiation doses to the skin can cause permanent hair loss, damaged sebaceous and sweat glands, atrophy, fibrosis, decreased or increased skin pigmentation, and ulceration or necrosis of the exposed tissue. However, similar lesions may develop later after much lower doses. Death from the cutaneous syndrome could result in days or longer, depending on other conditions, such as dose rate, medical care and size of injury.

Keywords: Cutaneous radiation syndrome- Ionizing radiation.

INTRODUCTION

Within 60 days after exposure to ionizing radiation an acute radiation syndrome (ARS) develops, with typical clinical signs and symptoms as a function of time. The interactions and combined effects of radiation induced damage to different organ systems are diverse, and not yet fully understood. Therefore, when accidental exposure to ionizing radiation is known or suspected, guidance for immediate diagnostic procedures and specialized care is required to handle the complexity of the acute radiation syndrome (ARS)\(^1\). The neurovascular system, the hematopoietic system, the cutaneous system, and the gastrointestinal are of critical significance for the development of ARS and should therefore receive a special attention in the medical management of radiation accident cases \(^2\).

Cutaneous radiation injury (CRI) is injury to the skin and underlying tissues from acute exposure to a large external dose of radiation. Acute radiation syndrome (ARS), the systemic manifestations of a large dose of ionizing radiation, will usually be accompanied by some skin damage; however, CRI can occur without symptoms of ARS. This is especially true with acute exposures to beta radiation or low-energy x-rays. These types of radiation are less penetrating and less likely to damage internal organs and cause ARS, but are still able to damage the skin (gamma radiation is the most common cause of ARS as it penetrates deeply into the tissues). CRI can occur with radiation doses as low as 2 Gray (Gy) or 200 rads and the severity of CRI symptoms increases with increasing doses. Most cases of CRI have occurred when individuals inadvertently come in contact with unsecured radiation sources from food irradiators, radiotherapy equipment, or well depth
gauges. In addition, cases of CRI have occurred in people who were overexposed to x-radiation from fluoroscopy units (3). Early signs and symptoms of CRI are itching, tingling, or a transient erythema or edema without a history of exposure to heat or caustic chemicals. Exposure to radiation can damage the basal cell layer of the skin and result in inflammation, erythema, and dry or moist desquamation. In addition, radiation damage to hair follicles can cause epilation. Transient and inconsistent erythema (associated with itching) can occur within a few hours of exposure and be followed by a latent, symptom-free phase lasting from a few days to several weeks. After the latent phase, intense reddening, blistering, and ulceration of the irradiated site are visible. Depending on the radiation dose, a third and even fourth wave of erythema are possible over the ensuing months or possibly years. In most cases, healing occurs by regenerative means; however, high radiation doses to the skin can cause permanent hair loss, damaged sebaceous and sweat glands, atrophy, fibrosis, decreased or increased skin pigmentation, and ulceration or necrosis of the exposed tissue (4).

The cutaneous syndrome has recently been named, and it may exist along with the others when the skin is exposed to a very high dose. Such high skin doses, in the absence of lethal whole-body irradiation, arise when exposing the skin to weakly-penetrating beta-emitting radioactive material, and these are known as “beta burns” (5, 6, 7).

New technologies and research during the past 20 years have provided a great understanding of the complex nature of radiation injury at molecular, cellular, tissue and organ system levels. The experience gained both in radiation therapy and in medical care of radiation accident patients has enabled development and use of new assessment and treatment modalities and provided more information about complications and numerous problems yet to be solved (8).

Although radiation accidents are not common, human error, failure to follow safety precautions and inadequate control or regulation of radiation sources have led to deaths and significant exposures among workers and members of the public.

Physicians practicing occupational medicine may be involved in immediate assessment and care of radiation accident victims. Under ordinary circumstances, they would not be involved in the treatment phase of the acute radiation syndrome (ARS) or serious local injuries, although they might be called on to explain procedures or prognoses to patients and their families. Their knowledge of triage, assessment, initial diagnostic methods and general treatment protocols, however, would be of great value in any radiation accident or incident involving harm to individuals. With CRI, the visible skin effects depend on the amount of the dose and the depth of penetration into the underlying tissues. Unlike the skin lesions caused by chemical or thermal damage, the lesions caused by radiation exposures may not appear during hours or even days following exposure, and burns and other skin effects tend to appear in cycles. In most cases, healing occurs by regenerative means; however, high radiation doses to the skin can cause permanent hair loss, damaged sebaceous and sweat glands, atrophy, fibrosis, decreased or increased skin pigmentation, and ulceration or necrosis of the exposed tissue (9).

Pathophysiology

The appearance of a cutaneous lesion can be indicative of the target tissue involved in the exposure. Erythema and moist desquamation are arguably the most documented phase of radiation induced damage to the skin. The target cell population, damage to which causes denudation of the epidermis, is the basal cells of the epidermis, including those cells situated within the canal of hair follicles. The reddening or erythema of the skin represents dilatation of the superficial blood vessels and is indicative of an inflammatory reaction (10).

Following irradiation with single doses of X-rays, for exposures just above or just below the threshold for the development of moist desquamation (15–25 Gy), cells are lost from the basal layer of the epidermis at a constant rate. Repopulation of the epidermis following irradiation with doses at the
The approximate threshold for moist desquamation is predominantly by the proliferation of surviving clonogenic basal cells from within the irradiated area (11). The labeling index of cells in these colonies after the injection of 3H-thymidine was between 30% and 40%. A high proportion of regenerating colonies has been found to be associated with the canal of hair follicles (12). The timing of the occurrence of moist desquamation is thus defined by the total turnover time of the epidermal structure exposed and is not influenced by the magnitude of the radiation dose.

Earlier denudation of the epithelium, shorter than the normal turnover time, occurs when basal cells and more specifically post-mitotic suprabasal cells are killed directly by irradiation after very high dose exposures. High dose, localized irradiation of the epidermis, without comparable effects on deeper dermal layers, occurs as a result of exposure to low energy β-emitters. In this situation the primary energy absorption will be in the viable layers of the epidermis above the basal layer. There may be an ~80% reduction in dose across the epidermis. Cells in the post-mitotic, but viable, upper layer of the epidermis will receive a significantly higher dose than stem cells in the basal layer and within the shaft of hair follicles (10).

A late phase of discoloration in moderately exposed areas is characterized by skin with a dusky or mauve appearance after 8–16 weeks (13, 14). The ischaemic appearance of the skin was confirmed by measurements of reduced blood flow as well as by the presence of severe edema (15, 16). The occlusion of blood vessels at the base of the dermis, the deep dermal plexus at the junction with the fatty layer, by the proliferation of endothelial cells or as a result of thrombus formation, is thought to be a major factor in the pathogenesis of this late phase of damage (17). This late phase of erythema may fade or the skin may develop an ischaemic necrosis of the dermis and subcutaneous fatty tissue. An early dusky mauve appearance may develop after exposure of the skin to extremely high doses arising from the high β-ray component associated with some accidents. This may be indicative of development of an acute necrotic reaction. If denudation of the epidermis persists, secondary damage to the dermis will occur as a result of fluid loss, infection and trauma even in the absence of severe radiation induced damage to the dermis.

Such events are not unique to radiation induced epithelial denudation. Secondary ulceration of the dermis can only heal by site contraction and scar tissue formation. Since normal dermal structures cannot be reconstructed, radiation induced damage to the dermis, whether it is a consequence of high dose acute necrosis or delayed ischaemic necrosis can only heal to leave a fibrotic scar (18, 19). The rate of healing will depend on the surface area of the original skin site involved and the depth of the necrosis. The depth of necrosis depends to a large extent on the radiation dose and radiation quality. Additional factors, such as infection, may exacerbate the extent of the lesion (20). This kind of dermal and subcutaneous tissue injury is non-specific and resembles the lesions induced by heat, chemicals or surgical excision, which may equally lead to a fibrotic scar.

**Stages and grades of CRS**

CRI will progress with time in stages and can be categorized by grade, with characteristics of the stages varying by grade of injury, as shown in Table (1). (Adapted from references 21, 22, 23)

- **Prodromal stage** (within hours of exposure). This stage is characterized by early erythema (first wave of erythema), heat sensations, and itching that define the exposure area. The duration of this stage is from 1 to 2 days.

- **Latent stage** (1–2 days post exposure). No injury is evident. Depending on the body part, the higher the dose, the shorter this period will last. The skin of the face, chest, and neck will have a shorter latent stage than will the skin of the palms of the hands or the soles of the feet.

- **Manifest illness stage** (days to weeks post exposure). The basal layer is repopulated through proliferation of surviving clonogenic cells. This stage begins with main erythema (second
wave), a sense of heat, and slight edema, which are often accompanied by increased pigmentation. The resulting symptoms vary from dry desquamation or ulceration to necrosis, depending on the severity of the CRI.

- **Third wave of erythema** (10–16 weeks post exposure, especially after beta exposure). Exposed persons experience late erythema, injury of blood vessels, edema, and increasing pain. A distinct bluish color of the skin can be observed. Epilation may subside, but new ulcers, dermal necrosis, and dermal atrophy (and thinning of the dermis layer) are possible.

- **Late effects** (months to years post exposure; threshold dose ~10 Gy or 1000 rads). Symptoms can vary from slight dermal atrophy (or thinning of dermis layer) to constant ulcer recurrence, dermal necrosis, and deformity. Possible effects include occlusion of small blood vessels with subsequent disturbances in the blood supply (telangiectasia); destruction of the lymphatic network; regional lymphostasis; and increasing invasive fibrosis, keratosis, vasculitis, and subcutaneous sclerosis of the connective tissue. Pigmentary changes and pain are often present. Skin cancer is possible in subsequent years.

- **Recovery** months to years

<p>| Table (1): Grades of cutaneous radiation Injury |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin dose</th>
<th>Prodromal stage</th>
<th>Latent stage</th>
<th>Manifest illness stage</th>
<th>Third wave of erythema</th>
<th>Recovery</th>
<th>Late effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>I(C1)</td>
<td>&gt; 2 Gy (200 rads)</td>
<td>1-2 days post exposure Or not seen</td>
<td>no injury evident for 2-5 weeks post-exposure</td>
<td>• 2-5 weeks post exposure, Lasting 20-30 days: redness of skin, slight edema, possible increased pigmentation</td>
<td>not seen</td>
<td>complete healing expected 28-40 days after dry desquamation (3-6 months Post exposure)</td>
<td>possible slight skin atrophy</td>
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<td></td>
<td></td>
<td>• 6-7 weeks post exposure, Dry desquamation</td>
<td></td>
<td></td>
<td>• possible skin cancer decades after exposure</td>
</tr>
<tr>
<td>I(C2)</td>
<td>&gt; 15 Gy (1500 rads)</td>
<td>6-24 hours postexposure With immediate sensation of heat lasting 1-2 days</td>
<td>no injury evident for 1-3 weeks post-exposure</td>
<td>• 1-3 weeks postexposure; Redness of skin, sense of heat, edema, skin may turn brown • 5-6 weeks postexposure, edema of subcutaneous tissues and blisters with</td>
<td>• 10-16 weeks Post exposure, injury of blood vessels, edema, and increasing pain • epilation may subside, but healing depends on size of injury and the possibility of more cycles of erythema</td>
<td></td>
<td>possible skin atrophy or ulcer recurrence</td>
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<td></td>
<td></td>
<td>• possible telangiectasia (up to 10 years post-exposure)</td>
</tr>
<tr>
<td>Grade</td>
<td>Skin dose</td>
<td>Prodromal stage</td>
<td>Latent stage</td>
<td>Manifest illness stage</td>
<td>Third wave of erythema</td>
<td>Recovery</td>
<td>Late effects</td>
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<tr>
<td>III (C3)</td>
<td>&gt; 40 Gy (4000 rads)</td>
<td>4-24 hours postexposure, With immediate pain or tingling lasting 1-2 days</td>
<td>none or less than 2 weeks</td>
<td>moist desquamation • possible epithelialization later</td>
<td>new ulcers and necrotic changes are possible</td>
<td>can involve ulcers that are extremely difficult to treat and that can require months to years to heal fully</td>
<td>• possible skin atrophy, depigmentation, constant ulcer recurrence, or deformity • possible occlusion of small vessels with subsequent disturbances in the blood supply, destruction of the lymphatic network, regional lymphostasis, and increasing fibrosis and sclerosis of the connective tissue • possible telangiectasia • possible skin</td>
</tr>
</tbody>
</table>
Clinical Characterization

The clinical grading summarizes the extent of the damage to individuals and the corresponding prognosis. The CRS grading is interpreted in Table 2. Since most of the selected symptoms may occur or recur at different time points in the development of the CRS, different phases can be identified.

Table 2: The overall prognostic aspects of the acute CS on the basis of the clinical grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Extent of impairment</th>
<th>Prognosis</th>
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<tbody>
<tr>
<td>C1</td>
<td>Mild damage</td>
<td>Recovery certain</td>
</tr>
<tr>
<td>C2</td>
<td>Moderate damage</td>
<td>Recovery without deficit likely</td>
</tr>
<tr>
<td>C3</td>
<td>Severe damage</td>
<td>Recovery with deficit likely</td>
</tr>
<tr>
<td>C4</td>
<td>Critical/fatal damage</td>
<td>Recovery impossible or with serious deficit</td>
</tr>
</tbody>
</table>
Grading C1

C1 may start with a brief transient erythema and itching during the prodromal period (degree 1 symptoms). This usually subsides within 36 h of exposure (fig.1). A second wave of erythema, the true erythema, appears around 5 days after exposure and may last for few weeks. The latent period and duration of the true erythema are variable and the severity will not exceed degree 1. At a later time (20–30 days) the skin may appear very dry owing to the loss of sweat and sebaceous glands and may be associated with a dry, scaly desquamation (degree 1). Dry desquamation may also be a consequence of an inflammatory response, leading to transient epidermal hypertrophy in the late effect phase of the CRS. Recovery is certain and the lesions may disappear completely within a few weeks and these early lesions will not cause clinical late effects \(^{(26)}\).

![Fig. (1): Erythema and skin edema](image1)

Grading C2

C2 can be described as a moderate damage to cutaneous tissue. Erythema (in the prodromal phase as well as in the manifest illness phase) can be seen in isolated patches of \(<10\, \text{cm}^2\) that do not add up to more than 10% of the body surface (degree 2). This may be associated with mild swelling (degree 1–2) and blistering (degree 2) 5–10 days after exposure (fig.2). Rupture of these blisters causes desquamation (degree 2). Blisters, which occur later after exposure (around day 30), can result in moist desquamation (degree 2). However, moist desquamation can also appear without prior blistering as a consequence of depletion of the epidermal stem cells. Transient hair loss or thinning of the hair diameter may develop at around 14 days after exposure. Recovery without deficit is possible \(^{(27)}\).

![Fig. (2): Blistering](image2)
**Grading C3**

The severity of symptoms is more pronounced than in C2, resulting from damage to cutaneous tissue in isolated or confluent patches, which may add up to 10–40% of the body surface (erythema degree 3). In the manifest illness phase this is associated with severe swelling (degree 2–3) caused by increased vascular permeability and loss of fluids to the extravascular tissues. Blister may develop about 5 days after exposure (degree 2–3). Rupture of blisters may reveal dermal loss, the depth of which may vary (desquamation degree 2–3, or development of ulcer/necrosis degree 1–2) as shown in fig.3&4. With delayed healing this may progress even deeper. If moist desquamation heals slowly, this may progress to secondary ulceration due to further loss of dermal tissue (ulcer/necrosis degree 3). Given appropriate clinical support, recovery is possible but nonetheless the patient will experience deficits in the late effect phase such as alopecia, tissue contraction, fibrosis, pigment changes and increased vulnerability to trauma. Healed lesions are often susceptible to reopening \(^{(28)}\).

![Fig. (3): Moist desquamation.](image1) ![Fig. (4): Radiation ulcer](image2)

**Grading C4**

In C4 there is a critical damage to cutaneous and subcutaneous tissues in isolated or confluent patches that may add up to more than 40% of the body surface, with the involvement of underlying tissues (erythema degree 4 in the prodromal phase). In the manifest illness phase, this results from a combination of severe damage to epidermal, dermal and subcutaneous tissue, underlying muscles and perhaps bony structures. Usually there is no symptom-free interval. This category is associated with severe swelling (degree 3–4) caused by an increase in vascular permeability and loss of fluids to the extravascular space. Bullae develop within a few days after exposure (degree 4). Rupture of blisters (desquamation degree 3) will result in severe electrolyte loss. Acute necrosis (degree 3–4), as well as onycholysis (fig.5), will develop, among other symptoms; as a result of interphase death 10–14 days post irradiation. This is different to the degree 1–4 ischaemic necrosis that usually develops in the late effect phase of the CRS. These severe skin lesions contribute significantly to multiple organ failure. Recovery is almost impossible but highly dependent on the pattern and severity of damage. Specialized medical treatment is required. Even in the case of survival, severe deficits such as alopecia, fibrosis, pigment changes, increased vulnerability to trauma, thermal and pressure changes, subcutaneous sclerosis and keratosis will be inevitable (fig.6). The damage may be so severe that amputation of extremities needs to be considered. Specific attention must, at this point, be given to additional implications to the CS from other organ systems. Granulocytopenia may increase the risk of concomitant infections, but owing to an impaired immune function, the clinical symptoms may be overlooked. Thrombocytopenia may result inhaemorrhagic bullae and larger haemorrhages of the body surface. In deciding whether or not to undertake surgery, these effects should be taken into account\(^{(29)}\).
Diagnostic Methods

In addition to information obtained by observation, interrogation and inspection may be required, Table 3 lists diagnostic methods that may be relevant for the verification of the organ specific grading. These methods should also be considered as a starting point for further control and follow-up examinations. The best time for an examination depends on the characteristics of the symptoms and the method selected.

Table (3): Diagnostic methods of CRS

<table>
<thead>
<tr>
<th>Method</th>
<th>Relevance for the CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color photography</td>
<td>Relevant for the documentation of changes in CRS symptoms as a function of time. It should be performed in addition to a detailed description of the observed sign. Calibration is mandatory in each event when photographs are taken (e.g. white piece of paper).</td>
</tr>
<tr>
<td>Ultrasound (7.5–20 MHz B-scan sonography)</td>
<td>Frequently used, reproducible and non-invasive method for the evaluation of skin thickness, skin density, ulcer depth and the involvement of subcutaneous tissues (^{31-33}). 7.5 MHz sonography is a procedure for evaluation of dermis, subcutaneous fat tissue, muscle fascia and musculature. Furthermore, the depth of radiation fibrosis and ulcers can be determined by 7.5 MHz sonography (^{31-34}). The 20 MHz scanner with an axial resolution of about 80 μm and a lateral resolution of 200 μm is suitable for investigating epidermis, dermis and subcutaneous fat tissue up to a depth of about 10 mm. The depth of cutaneous radiation ulcers can be determined by sonography before and during therapy.</td>
</tr>
<tr>
<td>Thermography</td>
<td>Useful method for the quantification of the skin temperature and heat loss of the body (^{35}). The skin surface temperature and the heat emitted from the body surface are connected with the cutaneous vascular system and are indirect parameters for the vascularization of the skin. Techniques such as infrared thermography, microwave thermography and liquid crystal contact thermography are available. There is a significantly lower local skin surface temperature in patients with necrosis. A significant higher skin temperature was observed in patients with Inflammation(^{34, 35}).</td>
</tr>
<tr>
<td>Capillary</td>
<td>Non-invasive method for the qualitative and quantitative evaluation of the capillaries of the stratum papillare of the dermis (^{35}). The capillaries of the</td>
</tr>
</tbody>
</table>
Method | Relevance for the CRS
--- | ---
microscopy | Nail fold of fingers or feet are dilated in patients in the manifest stage of CS. The capillaries are smaller and rare in patients in the chronic stage of CRS\(^{(36)}\). Additionally, subungual splinter haemorrhages may be visible in distal parts of the nail bed in these stages\(^{(37)}\).

Profilometry | The most common method to quantify the skin topography in two and three dimensions\(^{(34)}\). Analysis of the vertical and horizontal distribution of the furrows gives information on the skin surface.

MRI | Non-invasive approach for the examination of the signal intensity of dermis, subcutaneous fat tissue, muscle and bone. Morphological changes can be discovered. The increase in the magnetic resonance signal intensity is the result of fluid in the tissue, which may be present through inflammation, edema or necrosis. A reduced tissue fluid content leads to a decrease in signal intensity\(^{(30,34)}\). With nuclear magnetic resonance imaging the extent of skin ulcers irradiation exposed patients can be evaluated. A disadvantage of this method, as currently used, is its lack of ability to discriminate between necrosis and inflammation.

Histology | Invasive method for the determination of skin changes related to CRS. The histology of the manifestation stage/subacute stage of CRS demonstrates dilated blood vessels, edema and multiple infiltrations mainly consisting of neutrophils and eosinophils. The histology of the chronic stage/late stage of CS is characterized by epidermal atrophy or hypertrophy, fibrosis of the dermis, rare lymphohistiocytic infiltrations, dilated blood and lymphatic vessels in the upper dermis, hypopigmentation and hyperpigmentation and a loss of hair follicles\(^{(30,34,36)}\).

### Treatment of cutaneous radiation syndrome

The primary goal of treatment is the interruption of radiation-induced inflammation of the dermis. In view of a lack of controlled therapeutic trials, treatment is guided by inference from the standard care for nonradiation-induced skin injury, as recommended by dermatologists and radiotherapists. The conservative therapeutic regime is summarized in table (4). Anti-inflammatory agents such as topical class II to III steroids (e.g., betamethasone, mometasone), topical antibiotics, and antihistamines should be considered. Silver sulfadiazine cream with nonadherent dressings may be useful for covering the outer layers of skin during the moist desquamation phase of cutaneous injury\(^{(30)}\).

Treatment has to focus on the particular stage of CRS and the avoidance of additional risk to the patients\(^{(36,37)}\). The prodromal and manifestation stages are characterized by inflammatory processes. Anti-inflammatory creams, e.g., linoleic acid cream, should be used as the basic treatment. Additionally, nonatrophogenic local steroids should be used to reduce the inflammation. Systemic steroids (0.5–1.0 mg/kg prednisolone equivalent) should be applied in patients with extensive affected skin areas after contraindications have been checked to reduce dermal and muscular vasculitis. If the patients suffer from pain, analgesics should be given. Treatment with loratadine, a non-sedative and mast cell stabilizing antihistamine, provides a marked relief of a burning itch. Additional therapeutic modalities reported to be of value in the manifestation stage are antibiotics for bacterial infections and, if there are no contraindications, heparinization\(^{(36-39)}\).

Xerosis is one of the symptoms of the chronic stage of CRS. Basic therapy with a specific ointment containing linoleic acid may reduce the severity of initial transdermal fluid losses.
Teleangiectasias, which cause discomfort owing to a burning itch and heat sensation, may disappear after argon laser therapy.\(^{(36-38,40)}\)

Tretinoin cream 0.005%, applied once daily, can lead to clearance of focal and patchy radiation keratoses. In more extensive lesions, oral application of retinoids is recommended \(^{(36-38)}\).

Radiation fibrosis is characterised by an increase in the production of collagen fibres by affected fibroblasts. If left untreated, persistent cutaneous fibrosis may give rise to ulcerations. Various approaches have been undertaken to antagonise this chronic inflammatory process, including systemic and topical application of superoxide dismutase, systemic application of pentoxifylline and alphatocopherol and proteinase inhibitors\(^{(41-44)}\).

Interferon gamma inhibits collagen production by human dermal fibroblasts \(^{(45)}\). Interferon gamma should be scheduled on a low dose regimen, \((2–3) \times 100 \mu g/week\) s.c. for 6 months, then once per week for another 6 months. A decrease in skin thickness could be observed 6 months after initiation of therapy \(^{(45)}\).

Cutaneous radiation ulcers should be treated with topical dressings of tetrachlorodecaoxide (TCDO), which can induce considerable granulation and reepithelisation of ulcers. Additionally, hydrocolloid dressings or topical thrombocytic growth factors can be used \(^{(36, 37)}\). A recent interesting alternative is a wound dressing composed of semi-permeable fibres. A systematic evaluation of this new approach is pending. Integra, another semi-synthetic skin equivalent, has been used effectively to cover surgically removed areas of radionecrotic skin \(^{(46)}\).

Ucers, localized necrosis, and severe intractable pain are best treated by surgical excision and skin grafts \(^{(47)}\). Extensive tissue damage requires grafting with artificial skin, split-thickness skin grafts, or donor skin grafts \(^{(48)}\). All necrotic tissues must be removed to maximize the success of engraftment. Once hemostasis is achieved, a split-thickness graft is applied and secured using sutures, staples, or fibrin glue \(^{(49)}\). Multiple grafts may be required, and prolonged hospitalization should be anticipated.

Skin flaps are useful when additional reconstructive surgery (for tendon repair, nerve repair, and so forth) is required or when coverage of bone, cartilage, tendons, nerves, or blood vessels is necessary \(^{(50)}\). Flaps should also be used to cover severely scarred areas that are unable to support grafts. Amputation may be required for patients with a necrotic extremity \(^{(51)}\). If the indication is clear, amputation should take place as soon as possible after medical stabilization is achieved.

<table>
<thead>
<tr>
<th>Table (4): Conservative skin treatment relevant at different times after exposure</th>
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<tbody>
<tr>
<td><strong>Stage</strong></td>
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<tr>
<td>Prodromal stage (first week after exposure)</td>
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<td>Manifestation/subacute stage (days 8–60 after exposure)</td>
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<tr>
<td>Chronic stage and late stage (beyond day 60 after exposure)</td>
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New Emerging Concepts in the Medical Management of Local Radiation Injury

Treatment of severe radiation burns remains a difficult medical challenge. The response of the skin to ionizing radiation results in a range of clinical manifestations. The most severe manifestations are highly invalidating. Although several therapeutic strategies (excision, skin grafting, skin or muscle flaps) have been used with some success, none have proven entirely satisfying. The concept that stem cell injections could be used for reducing normal tissue injury has been discussed for a number of years. Mesenchymal stem cells (MSC) therapy may be a promising therapeutic approach for improving radiation-induced skin and muscle damages. Pre-clinical and clinical benefit of mesenchymal stem cell injection for ulcerated skin and muscle restoration after high dose radiation exposure has been successfully demonstrated (52).

The efficacy of MSC treatment in promoting skin regeneration has been shown in multiple preclinical injury models, including laceration (53), thermal burn (54), and radiation exposure (55-57). The results of these studies demonstrate more expedient wound closure, decreased incidence of infection, increased vasculogenesis and elasticity, and reduced scar formation. Lacerative injury concurrent with irradiation presents a daunting treatment challenge. This scenario has been specifically evaluated by Hao et al. (58).

Evidence that MSCs play a natural role in the process of skin regeneration in humans has been collected in a clinical study, in which the number of MSCs circulating in the peripheral blood of thermal-burn patients was quantified and compared to the number of circulating MSCs in the blood of healthy volunteers (59). MSC phenotype was determined by the positive expression of five specific cell surface markers and the negative expression of eight other markers. The percentage of MSCs in circulating blood was more than 20-fold greater in burn patients compared to that in healthy individuals, and the degree of increase was correlated with the size and severity of the burn. These results offer data from human subjects that suggest MSCs play an important role in skin regenerative processes because the cells appear to be mobilized from the bone marrow in response to injury (60).

CONCLUSION

Early diagnosis and dose assessment are important when persons are accidentally or intentionally injured by ionizing radiation. The cutaneous syndrome may develop early following exposure (e.g., 1–2 days). However, it may take years before becoming fully manifest. Early lesions include erythema, edema, and dry desquamation of the skin. More advanced lesions include bullae, moist desquamation, ulceration, and onycholyis. Ulceration may be limited to the epidermis or may involve deeper structures, such as dermis, subcutaneous tissue, and even muscle and/or bone.

There are many aspects to consider when diagnosing and managing radiation exposed patients. Acute versus chronic effects can be differentiated by the latency of manifestation of the radiation effects. Since acute effects require immediate therapeutic intervention, they should be diagnosed at an early stage. Therefore, all efforts must be made to reduce the individual exposure to ionizing radiation and, thus, the absorbed dose.

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