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Cutaneous radiation syndrome in multi-organ failure

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Abstract. The likelihood of an individual being exposed to, and thus the probability of cutaneous injury from, nuclear weapons or dispersed nuclear material has, in contrast to post cold war euphoria, considerably increased during the last 13 years. This is in part due to a temporary loss of control of nuclear material, including uncontrolled deployment, and in part to an increasing capability and apparent willingness of terrorist and other criminal groups to use such material for their purposes. A relatively recent danger emerges from the development of so-called robust nuclear earth penetrators (RNEPs) to destroy very deep bunkers, which may be used in future "conventional" wars, and which without doubt will cause contamination with short-range radioactive nuclides, which will primarily affect the skin. In summary, the probability of local cutaneous radiation exposures to extremely high absorbed doses (<60 Gy), with concomitantly survivable bone marrow doses, has increased.

The pathophysiology of cutaneous radiation reactions

Ionising radiation leads to long-term impairment of various physiological functions that have been reported over several decades. However, with regard to skin injuries, recent scientific progress has slightly altered general concepts of the pathophysiology of cutaneous radiation injuries, with a decisive impact on diagnosis, treatment and follow-up.

In contrast to older concepts, ionising radiation does not only affect the proliferative capacity of cutaneous or epidermal stem cells, but also modulates the communicative network of epidermal keratinocytes, dermal fibroblasts, and circulating and resident immunocompetent cells, such as Langerhans cells, dermal dendritic cells, and both neutrophilic and eosinophilic granulocytes and lymphocytes. The concept of the cutaneous radiation syndrome (CRS), as it was defined a decade ago [1], thus combines antiproliferative effects with those of local inflammatory reactions occurring in a characteristic temporal pattern. In the initial phase, a few hours following irradiation, a transient and inconsistent erythema may occur — the prodromal erythema — which additionally may be associated with an itching sensation. In this early phase, transcriptional activation of pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-3, IL-5, IL-6 and tumour necrosis factor-α (TNF-α), in keratinocytes, and of chemokines such as IL-8 and eotaxin in both epidermal keratinocytes and dermal fibroblasts occurs. The latter induces the induction of adhesion molecules such as ICAM-1 on keratinocytes and dermal endothelial cells as well as V-CAM and E-selectin on endothelial cells, as identified *in vitro* and *in vivo* [2–4]. This transcriptional activation of pro-inflammatory cytokines leads to the release of anti-inflammatory cytokines on the other side, most importantly transforming growth factor-β (TGF-β). As long as there is equilibrium between pro- and anti-inflammatory processes, a clinically asymptomatic condition, denominated the latency phase, results. The duration of this latency phase as well as the intensity of the subsequent clinical sequelae depend on the amount of damage induced by radiation exposure and are thus, within certain margins, dose dependent. Within days to a few weeks, the manifestation stage may occur. In this stage, intense reddening, blistering and ulceration of the irradiated site will be discernible. At this stage the tissue destruction, specifically of the upper epidermal layer, is associated with a capillaritis and vasculitis of the dermal venules and arterioles and an infiltrate of neutrophil and eosinophil granulocytes, leading to a complex wound. This may either be confined to the epidermis and upper dermis or may penetrate through the subcutaneous fatty tissue to the musculature. Subepidermal blistering is a result of both apoptosis and the necrotic breakdown of epidermal tissue. Following this stage, a vasculitis of the deep dermal and subcutaneous blood vessels results in a bluish-red colouration of the affected skin [5]. In consequence, all these processes result in considerable tissue damage, which, however, is not present from the onset but develops due to the described inflammatory reactions, for which the radiation exposure may act as an initiating process (Figure 1).

In contrast to thermal burns or the consequences of cutaneous contamination with chemical toxic agents, these wounds do not develop immediately, but evolve over several days to weeks, dependent on the initial radiation dose and the individual's radiation sensitivity.

With a latency of 3 months to 2 years, a dermal and subcutaneous fibrosis may occur at the site of radiation exposure. This fibrosis, which is progressive by nature, may be very prominent and lead to complete disappearance of the subcutaneous fatty tissue, so that in advanced cases a direct continuation from the dermis to the underlying muscle fascia will be observed.

In this phase, a scarce perivascular infiltrate, composed primarily of CD4+ lymphocytes, can be seen histologically (Figure 2).

In this phase, TGF-β is transcriptionally activated at high levels. This is the result of a cascade in activation of smad transcription factors [6].

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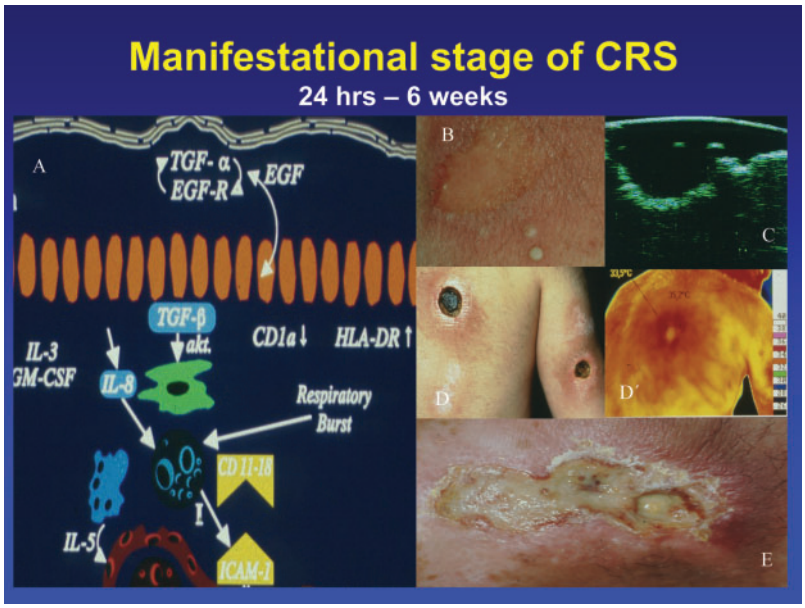

Figure 1. Manifestation stage of the cutaneous radiation syndrome (CRS). (A) Schematic drawing of the pathophysiological processes involved. (B) Clinical aspect of a manifestation stage, 24 h after accidental exposure of the lateral thorax to a cutaneous dose of 60 Gy of photons. An eroded blister and sterile pustules can be seen (iatrogenic accident in Germany, 1994). (C) High frequency ultrasound of manifestation stage on the upper arm, showing decreased dermal echogenicity as a sign of inflammatory interstitial oedema (Georgian accident, 1997). (D) Thermographic images of the back of a victim with an inflammatory reaction (Courtesy of Prof. J M Cosset, Institut Curie, Paris) (Georgian accident, 1997). (E) Ulcerative manifestation stage, suprapatellar region (Georgian accident, 1997).

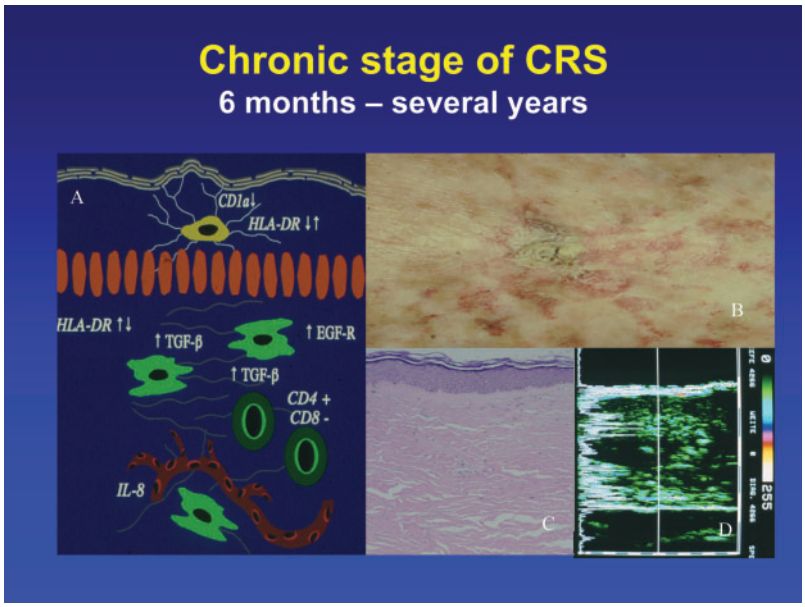

Figure 2. Chronic stage of the cutaneous radiation syndrome (CRS). (A) Schematic drawing of the pathophysiological processes involved. (B) Clinical aspect of the chronic stage, 6 years after exposure (lower leg of a survivor of the accident in Chernobyl (1986), documented 1992). Note the focal radiation keratosis (benign on biopsy), telengiectasias and severe fibrosis next to epidermal atrophy. (C) Histopathology of radiation fibrosis: loss of epidermal rete-ridges, flattening of the epidermis, homogeneous collagenisation and scarce perivascular lymphocytic infiltrate. Biopsy taken from the back of a Chernobyl survivor in 1993. (D) High frequency ultrasound of chronic stage (lower leg of a Chernobyl survivor, documented in 1993) prior to treatment with interferon-γ. An extremely increased echogenicity from the epidermal entrance echo down to the muscle fascia indicates severe radiation fibrosis.

Several years to decades after exposure, chronic sequelae appear, such as severe xerosis (dryness) of the skin owing to loss of sebaceous and sweat glands, alopecia and increased transepidermal water loss. This results in an increased vulnerability of the skin, often leading to secondary ulceration [7]. Neoplastic transformation may develop over several years at the irradiated site, with squamous and basal cell carcinomas, sometimes preceded by radiation keratoses. However, this aspect of accidental exposure is often overestimated. Based upon published literature and our own experience in the treatment and follow-up of accident survivors, secondary malignancies generally do not occur in the areas of maximum exposure and severe clinical consequences, but rather in locations without any signs of deterministic effects, which would correspond to absorbed single doses between 1 Gy and 10 Gy.

The abovementioned features are summarised in Table 1.

Clinical features and diagnostic difficulties of the CRS

The effects of physical damage to the skin generally result in a common final phase; once tissue integrity has been dissolved, it is impossible to discriminate between a thermal burn, a chemical toxic reaction or radiation injury. It is the time sequence of events that makes the difference in the acute phase. In the chronic stage, it is the progressive nature of radiation fibrosis that renders this reaction different from scarring of a thermal burn or a severe toxic reaction to a chemical agent. It may be considered as the characteristic trait of the CRS that the reactions occur in a delayed pattern. This implies that the clinical reactions following an accidental radiation exposure may remain unnoticed, and the patient presents only a couple of days or even weeks later with the symptoms of the manifestation stage. It may then be extremely difficult to identify the reaction as a case of

Table 1. Stages of the cutaneous radiation syndrome (according to Second Consensus Development Conference on the Management of Radiation Injuries, Bethesda, MD, 1993)

Stage	Name and onset	Symptoms	Old synonyms
I	Prodromal (24–72 h)	Transient erythema, itch	Early erythema
II	Manifestation (days–4 weeks)	(a) Intense erythema/dry scales	Main erythema/radiodermatitis/dry–moist desquamation/radionecrosis
		(b) Blisters, erosions, pain	
		(c) Ulcerative necrosis	
III	Subacute (4–6 weeks)	Subcutaneous vasculitis	(Dusky mauve erythema in pig skin model)
IV	Chronic (3 months–2 years)	Epidermal keratosis, atrophy, subcutaneous fibrosis, telengiectasias, ulceration	Chronic radiodermatitis late ulceration Radiation scar

CRS — a feature that has occurred globally in almost every major radiation accident in the last 15 years. Owing to its transient nature, the prodromal erythema may easily be overlooked. If there is a suspicion of local cutaneous exposure to ionising radiation, prodromal erythema should be looked for and documented, ideally by photography. Although the extent and intensity of the prodromal erythema are not predictive for the intensity of the manifestation or chronic stages to be expected, it does give valuable information regarding where the maximum clinical reaction will occur.

Physical and in most instances, biological dosimetry are generally grossly overestimated with respect to their relevance for the clinical management of the CRS, apart from the fact that they may prove that an exposure has in fact occurred. The reason for this is the basic circumstance: a clinically relevant cutaneous radiation reaction must be the result of an extremely inhomogeneous partial body exposure, mostly with short-range nuclides, as clinically relevant cutaneous reactions will generally be expected above a single dose of 15 Gy. A total body exposure with deeply penetrating radiation of that dose would be lethal due to the development of haematopoietic and/or gastrointestinal radiation syndrome. On the other hand, a local exposure to such a dose at, for example, the upper thighs would not necessarily cause major alteration of tooth enamel or a total body counter, which might be used for physical dosimetry. A bone marrow count or searching for chromosomal alterations of lymphocytes may, in this case, not reveal major alterations, as they will rather reflect an average of the bone marrow or lymphocytes of the whole organism. Therefore, although recently it could be shown by multicolour fluorescence *in situ* hybridisation (M-FISH) that irradiated human dermal fibroblasts reveal comparable chromosomal aberrations to irradiated lymphocytes, the diagnosis of CRS remains a clinical one.

During the manifestation and subacute stage, the extent of tissue involvement, but not necessarily damage, can be detected by high frequency ultrasound and magnetic resonance imaging (MRI). The latter method can be combined with contrast enhancement by injected gadolinium. This, however, gives only a hint to the extent of the inflammatory reaction, but does not mean that the imaged tissue is also necrotic. This has important therapeutic implications as, in contrast to older concepts, the whole tissue should not be surgically resected. An additional, non-invasive method to reveal the extent of cutaneous involvement in the manifestation and subacute stage is thermography, which has been used with success in a variety of accidents.

In the chronic stage, fibrosis is the predominant symptom, which causes additional distress to the patient as it may lead to further tissue breakdown (late ulceration), mechanical impairment of members and joints and muscular atrophy. It can be quantified both by high frequency ultrasound and MRI. Epidermal atrophy, pigment changes and focal radiation keratoses, together with an increased epidermal water loss and a severe xerosis, contribute to a highly vulnerable skin that requires continuous support and follow-up.

Telangiectasias, although generally a cosmetic problem, may become a nuisance to the patient if they are very extensive; the resulting cutaneous hyperaemia leads to burning mis-sensations in the affected areas.

Organ involvement is generally a result of a mixture of total body and inhomogeneous partial body exposure. Here, extensive cutaneous involvement can severely affect the function of otherwise intact organs, such as renal failure due to toxic shock syndrome; and radiation-depleted organs (bone marrow, gastrointestinal tract) can influence the course and severity of the CRS. For a thorough evaluation under accident conditions, the response category concept has been developed (see [8] in this issue).

Table 2 summarises the potential interdependencies between CRS and organ involvement.

Table 2. Interdependencies between cutaneous radiation syndrome, multi-organ failure and inhomogeneous radiation exposure

Primary	Distinct radiation-induced functional impairment in organ systems (gastrointestinal tract, liver, heart, kidneys, skin)
Secondary A	Organ failure due to radiation-induced alterations of skin function (*e.g.* renal insufficiency due to extensive cutaneous necrosis)
Secondary B	Cutaneous alterations due to radiation-induced organ failure (*e.g.* cutaneous oedema due to radiation nephropathy, cutaneous fluid loss due to gastrointestinal syndrome, viral cutaneous infections due to haematopoietic syndrome)

Diagnostic and therapeutic consequences

Although a lot of research has been carried out in the last few decades to identify unequivocal indicators for a radiation exposure incident and to discriminate it from other physical effectors, to date a really specific indicator has not been found. Recently, chromosomal deletions and translocations have been identified in primary irradiated human skin fibroblasts. These are identical to those that have for a long time been described in lymphocytes. These may well serve as an indicator for partial body exposure at a time when clinical signs of CRS have not yet appeared and may open a new window of opportunity for causal-oriented treatment of cutaneous radiation injuries at an early stage.

In the prodromal stage of CRS, antihistamines and topical antipruriginous preparations may be used. Antihistamines do not only act against itch, but also reduce induction of adhesion molecules on keratinocytes and endothelial cells and thus help to prevent or attenuate initiation of the vicious circle, which finally leads to the manifestation stage.

The latency phase between prodromal erythema and manifestation stage, which is by definition without clinical symptoms, is the optimal phase for secondary prophylaxis. Owing to the substantial inflammatory component of the manifestation stage, medium to high dose systemic glucocorticosteroids (methylprednisolone equivalent of 0.5–1.5 g kg^{-1} body weight day^{-1}) should be combined with effective topical anti-inflammatory treatment with class III to class IV steroids. Whether there is a place for the new topical anti-inflammatory drugs such as tacrolimus and pimecrolimus, which is theoretically very probable, remains to be determined in practice [9].

Once the manifestation stage has developed, an additional threat is presented by bacterial, fungal and viral infections. Repeated swabs to identify this super infection as early as possible and to monitor the efficacy of antibiotic treatment are necessary. The indication of antibiotic prophylaxis will mainly depend on additional symptoms such as radiation-induced bone marrow suppression or a simultaneously occurring gastrointestinal syndrome.

Blisters, if sterile, should be punctured, but not removed as long as they are intact. In the case of necrosis, thorough but cautious debridement should be carried out. Apart from using a conventional scalpel, better results may sometimes be achieved using an infrared ablative laser or a high-pressure water scalpel (own unpublished data).

Topical treatment comprises the application of wet dressings, and later alginates and hydrocolloids. Growth factors such as platelet-derived growth factor (PDGF; Regranex^{TM}) and keratinocyte growth factor (KGF; not yet formally approved) may be used to foster granulation and epithelialisation; however, this will require thorough bacterial decontamination of the surface defects to be effective. Surgical procedures require a defined analysis of the extent of disease by MRI and high frequency (20 MHz) ultrasound. In the case of positive MRI, anti-inflammatory treatment with 0.5–1 mg of methylprednisolone is warranted prior to surgical excision, in order to avoid too extensive resection [10]. If cutaneous and muscle layers are affected and surgical resection is unavoidable, temporary coverage with the synthetic skin equivalent Integra^{TM} has proven very effective (M Carsin, pers. comm.). If further granulation has been reached, closure with full-thickness or split skin grafts as well as with cultured and reconstituted skin is possible.

In the subacute stage, heparinisation to prevent sludging of dermal and subcutaneous vessels in addition to anti-inflammatory treatment has been claimed to be helpful.

In the chronic stage, fibrosis is the predominant clinical problem. In contrast to former guidelines, which considered radiation fibrosis as an entity that was impossible to treat by means other than surgery, a variety of different options have been developed in the last few years for conservative treatment of radiation fibrosis. Apart from bovine manganese superoxide dismutase [11], which for obvious reasons is not available at present, oral administration of pentoxifylline (400 mg three times daily) and vitamin E (400 mg once a day), initially reported as a case description [12], has been proven to be effective in a controlled trial [12, 13] on patients suffering from fibrosis following radiation therapy.

In an open trial on survivors of the Chernobyl radiation accident as well as on five patients suffering from cutaneous fibrosis after radiation therapy [13–17], subcutaneous injection of interferon-γ (Imukin^{TM}) has been demonstrated to reduce pre-existing fibrosis to almost normal values. These options should be carefully considered before excision of larger fibrotic plaques and streaks.

Radiation keratoses are focal tight keratotic lesions, indicating an increased cornifying activity of epidermal keratinocytes. In some instances these keratoses represent pre-cancerous lesions, although few data exist regarding the factual quantitative component of transformation. In any case of clinical doubt, excisional biopsy and histological assessment of the lesions to exclude squamous cell carcinoma should be performed.

Telengiectasias may be treated effectively with argon, diode or dye lasers, without any relevant side effects or sequelae (own unpublished observations).

Basal cell and squamous cell carcinomas are long-term stochastic sequelae of cutaneous radiation exposure, which may occur in areas that did not necessarily show any symptoms of CRS immediately after exposure [18]. This is in contrast to malignant melanoma, which has never been demonstrated conclusively to follow cutaneous radiation overexposure [19]. As latency periods may be years or decades, a long-term if not life-long follow-up of radiation-exposed patients is necessary [20].

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