Anatomy of the Skin and Pathophysiology of Radiation Dermatitis

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2.1 Anatomy of the Skin

2.1.1 The Epidermis

The outermost layer of the skin is the epidermis, which is primarily made up of keratinocytes (Fig. 2.1). Keratinocytes produce the keratin protein that serves as the major structural component of the epidermal barrier.

2.1.1.1 The Stratum Basale

The deepest layer of the epidermis is the basal layer, which contains rounded keratinocytes that continually divide to replenish the epidermis. As the cells divide, some retain their replicative potential and others become transit amplifying cells that mature into squamous keratinocytes. These push older cells up toward the surface of the skin, where they are shed. Malignant transformation of basal keratinocytes leads to basal cell carcinoma.

Embedded among the basal keratinocytes are melanocytes, the cells that produce the pigment of the skin. Melanin functions to protect the skin from ultraviolet radiation. Production of melanin is stimulated by UV or other injury to the skin, leading to tanning, freckling, or age spots. Malignant transformation of melanocytes leads to melanoma.

The basal layer also contains Merkel cells, which are tactile sensory cells of neuroectodermal origin. Malignant transformation of these cells leads to Merkel cell carcinoma.

2.1.1.2 The Stratum Spinosum

Just superior to the basal layer is the spinous layer or squamous layer, the thickest layer of the epidermis. This layer is characterized by polygonal keratinocytes, interspersed with Langerhans cells. These are cells of the immune system that detect foreign antigen.

2.1.1.3 The Stratum Granulosum and Stratum Lucidum

As keratinocytes continue to mature and progress toward the outer surface of the skin, they become larger and flatter. The stratum granulosum or granular layer is characterized by basophilic keratohyalin granules that bind keratin together, resulting in a dense barrier layer. These cells also contain lamellar bodies containing lipids and proteins that are secreted into the extracellular space to provide the hydrophobic lipid envelope of the skin. Clearing of these keratinocytes forms the stratum lucidum. These cells ultimately fuse together and die, transitioning into the stratum corneum.

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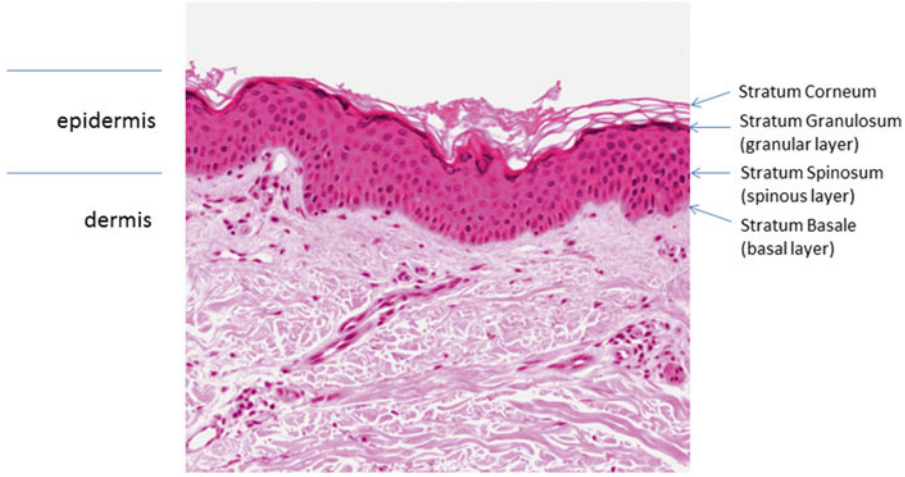


Fig. 2.1 Diagram of the skin. Photo shows normal arm skin, 100×. Photo courtesy of John Geisse, MD

2.1.1.4 The Stratum Corneum

The outermost later of the epidermis is made up of multiple layers of dead keratinocytes. The stratum corneum is continuously sloughed off as underlying keratinocytes mature and take their place. The entire epidermal turnover takes approximately 4 weeks in younger people and 5–7 weeks in older people.

2.1.2 The Dermis

The dermis lies beneath the epidermis and is the thickest layer of the skin. Its main function is to regulate body temperature and supply the epidermis with blood. The dermis is primarily made up of collagen and elastin produced by fibroblasts. Collagen supports the skin with structural durability, while elastin provides skin flexibility and elasticity. The dermis contains a papillary outer layer and a reticular inner layer, which are primarily distinguished by the density of collagen and the specialized structures within. Specialized structures include blood vessels, lymphatics, pain and touch receptors, hair follicles, and sebaceous glands.

2.2 Radiation Skin Reactions

2.2.1 Acute Radiation Dermatitis

Ionizing radiation exposure results in non-visible or prodromal erythema of the skin within 24 h of exposure. It is followed by a second visible phase of erythema beginning 10–14 days after exposure and lasting for up to 1 month [1, 2]. Acute radiation dermatitis is characterized by erythema, edema, blistering, and erosion of the skin. There is often tanning or darkening of the skin preceding desquamation and slough. This reaction usually resolves, but the skin that receives large doses of radiation will typically lose adnexae including hair follicles and eccrine and sebaceous glands. The skin may have permanent telangiectasia, mottled pigmentation, dry texture, and alopecia. Less common presentations of acute radiation dermatitis include morbilliform rash, annular or ring-shaped lesions, and bullae or blisters.

The erythema results from an increased blood supply via the dermal vascular plexus, while dry desquamation results from the inability of basal keratinocyte replication to proliferate fast enough

to replenish the damaged squamous epithelium. Injury to sebaceous glands causes skin dryness and injury to follicles results in hair loss. Moderate to severe erythema is most common in skin folds or areas of friction and moist occlusion. Focal loss of the epidermis with a serious drainage and fibrinous exudate are characteristic of moist desquamation. Moist desquamation may be limited to skin folds (groin, axilla, or inframammary fold region) or appear confluent in locations other than skin folds. Bullae may develop. Areas of moist desquamation or ruptured bullae are susceptible to infection, especially with *Staphylococcus aureus*.

2.2.2 Histological Features of Acute Radiation Dermatitis

Acute radiation dermatitis is rarely biopsied, as the clinical presentation is typically sufficient to render the diagnosis. The histopathologic features include keratinocyte necrosis with spongiosis. There may be subepidermal vesiculation progressing to bullae or epidermal slough. Edema is present in the dermis and endothelial cells. Vasodilatation and erythrocyte extravasation may be present. Fibrin thrombin may obstruct arterioles [3]. The inflammatory infiltrate in the dermis includes lymphocytes, eosinophils, macrophages, and plasma cells. Hair follicles may shift into the catagen phase, resulting in synchronized but reversible hair loss. Hyperkeratosis is associated with dry desquamation.

2.2.3 Chronic Radiation Dermatitis

Radiation dermatitis is deemed chronic if the resulting changes appear after a latent period of months to years [4] or if they appear as an extension or progression of the acute process. An example of the latter is breast edema which may persist for several years after breast-conserving surgery and radiation and typically resolves after 2–3 years [5]. The most common chronic changes are hypopigmentation and telangiectasia, which can occur in over 80 % of patients who received moderate doses in the range of 40–50 Gy [6]. Hyperpigmentation, depressed scarring, induration, and keratosis (growths of keratin on the skin) are seen less commonly. Chronic changes typically continue to evolve over a period of about 4 years following treatment [7].

Changes in pigmentation (hypopigmentation or hyperpigmentation) which appear with acute radiation dermatitis may persist or gradually normalize. Textural changes in the skin include atrophic plaques, hyperkeratosis, and xerosis. Loss of hair follicles results in alopecia. If hair follicles have not been destroyed, the hair may be brittle. Telangiectasias are dilated superficial blood vessels. Their appearance has been correlated with the extent and severity of acute reactions with an increased incidence in areas of prior moist desquamation [8, 9]. They are permanent and tend to increase with time [5, 10]. Atrophy of the skin results in fragility and a predisposition to delayed or non-healing of ulcerations or insults to the skin and infection. Fibrosis and contraction result from injury to the fibroblasts. Radiation necrosis results from dermal ischemia and impairment of the reparative process. In this most severe process, superinfection is not uncommon and skin grafts may be required.

2.2.4 Histological Features of Chronic Radiation Dermatitis

Histopathologic examination of chronic radiation dermatitis demonstrates dermal sclerosis and elastosis (Fig. 2.2). The epidermal histology is variable, with hyperkeratosis, focal parakeratosis, atypia, and dyskeratosis. There may be basal vacuolar change and liquefactive degeneration.

Chronic radiation dermatitis is characterized by “radiation fibroblasts,” bizarre dermal fibroblasts with large atypical nuclei and basophilic cytoplasm. These may raise concern for malignant transformation, but they do not appear to have malignant potential. Radiation fibroblasts typically express factor XIIIa and may express CD34 [11]. Dermal blood vessels may dilate and become tortuous, particularly in high-grade dermatitis. This correlates with the telangiectasia

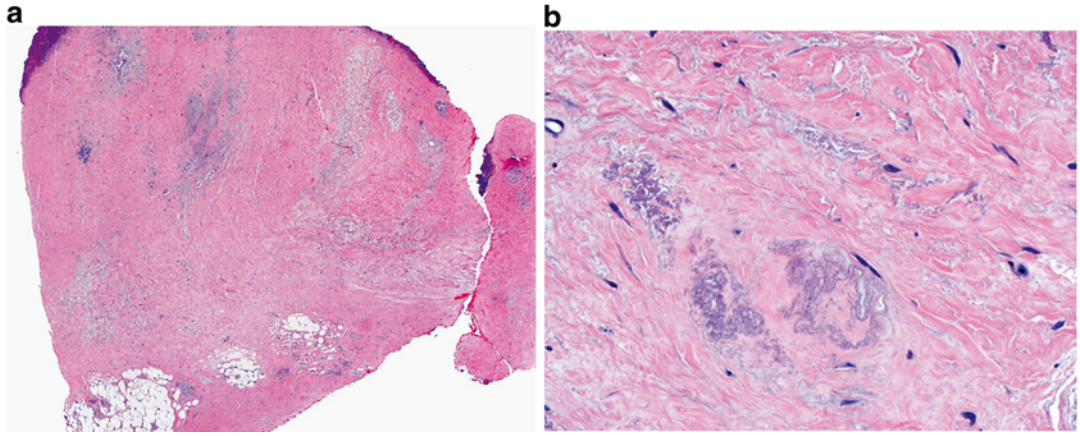


Fig. 2.2 Chronic radiation dermatitis. (**a**) 40×, (**b**) 400×. Photos courtesy of Jeffrey North, MD

and poikiloderma seen on clinical examination. Vessels are reduced in number and may have hyaline change and narrowing of the lumen. Ablation of the pilosebaceous unit results in irreversible alopecia, and there may be eccrine atrophy which results in loss of sweat formation. In contrast to thermal burns, the arrector pili muscles remain and are often surrounded by sclerotic collagen.

2.3 Pathophysiology of Radiation Dermatitis

Radiation dermatitis is the result of injury to multiple skin structures including epidermal keratinocytes, dermal fibroblasts, cutaneous vasculature, and hair follicles. It interferes with the maturation, reproduction, and repopulation of these cells [12]. It is the result of direct tissue injury as well as the inflammation recruited to the injured skin [13, 14]. DNA damage is mediated by the production of free radicals. Leukocytes and other immune cells migrate from the circulation to the skin [15, 16]. Increased formation of cytokines and chemokines (IL-1 alpha, IL-1 beta, TNF-alpha, IL-6, IL-8, CL4, CXCL10, and CCL2) has been associated with acute radiation dermatitis [15, 17, 18]. Radiation causes immediate direct injury to keratinocytes, which results in oxidative stress. Production of free radicals such as reactive oxygen species superoxides, hydrogen peroxides, and hydroxyl radicals cause damage to the tissue [19]. This triggers vasodilation, vascular permeability, and recruitment of inflammatory cells. These immune cells secrete pro-inflammatory cytokines that drive fibroblast differentiation into myofibroblasts, which produce collagen and smooth muscle actin [20]. Extracellular matrix deposition by activated myofibroblasts results in wound healing, but persistent activation from repeated radiation injury can lead to fibrosis [21, 22]. Acute injury results from reduced and impaired stem cells, changes in endothelial cells, inflammation, and epidermal cell apoptosis and necrosis [13].

Fibrosis is primarily driven by transforming growth factor beta (TGFβ), which is upregulated in response to ionizing radiation [23, 24]. TGFβ plays a key role in tissue fibrosis by stimulating fibroblasts to secrete extracellular matrix proteins (connective tissue growth factor) [25]. TGFβ-induced fibrosis appears to be mediated via Smad3, as Smad3 knockout mice exhibit accelerated healing and decreased damage after irradiation [26].

Macrophages play a major role in radiation dermatitis and fibrosis. Macrophages may be activated by tumor necrosis factor alpha (TNFα) and interferon gamma (IFNγ) to polarize into an M1 pro-inflammatory phenotype producing IL1β, TNFα, IL-6, and IL-12 or may be activated by IL-4 and IL-13 to polarize into an anti-inflammatory phenotype marked by production of TGFβ [27]. The complex balance of these macro-

phage populations during radiation injury and tissue repair are not well understood and likely shift over time to promote resolution of inflammation and myofibroblast activity.

2.4 Radiosensitizers and Radiation Recall

Radiation recall skin reactions are precipitated by the administration of systemic agents. They occur in areas of acute skin reactions that had previously returned to normal and should not be confused with delayed healing. They are unpredictable and uncommon. The onset is typically within days to weeks after exposure to the inciting agent. It may appear as erythema, dry desquamation, vesicles, maculopapular lesions, and in severe cases ulceration and skin necrosis. Some of the agents which have been associated with radiation recall dermatitis include bleomycin, capecitabine, docetaxel, paclitaxel, cisplatin, cyclophosphamide, epirubicin, doxorubicin, actinomycin D, etoposide, 5-fluorouracil, gemcitabine, methotrexate, tamoxifen, and vinblastine [28].

In addition, numerous systemic agents can be used to augment the effect of radiation therapy (radiation sensitizers), including chemotherapeutic agents such as 5-fluorouracil, gemcitabine, capecitabine, and platinum analogs and targeted molecular inhibitors such as EGFR inhibitors [29, 30].

2.5 Other Skin Eruptions Associated with Radiation Therapy

A less common presentation of radiation dermatitis is the eosinophilic, polymorphous, pruritic eruption, often associated with radiation therapy for breast cancer. This eruption favors the extremities and may arise outside of the radiation field. There is a lymphohistiocytic infiltrate with eosinophils.

Other skin conditions that have been reported as arising within radiation fields include lichen planus, lichen sclerosus, morphea, graft vs. host disease, and pseudosclerodermatous panniculitis. Conditions that can be induced by radiation therapy and extend beyond the radiation field include erythema multiforme, bullous and cicatricial pemphigoid, herpes zoster, pemphigus vulgaris and pemphigus foliaceus.

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