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CUTANEOUS EFFECTS OF RADIOTHERAPY- A REVIEW ARTICLE

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ABSTRACT

Radiotherapy is a common modality in cancer treatment and more than 50 % of affected patients will eventually receive some form of radiotherapy as definite, preoperative, postoperative or palliative treatment.
Radiation induced skin changes were recognized soon after the discovery of x-rays and were scientifically reported as early as 1902. Even when the skin is not the primary target, it may be injured as an innocent bystander and develop profound alteration on functional, gross and molecular levels.
Radiotherapy can result in common, inevitable cutaneous side effects such as acute radiodermatitis, chronic radiodermatitis and skin cancers.
Acute radiation dermatitis manifests as erythema, edema, burning or tingling, pruritus, pigmentation, desquamation, epilation, shedding of nails, vesiculation or bulla formation, erosion or ulceration. Chronic radiation changes include excessive wrinkling or atrophy of the skin, hyperpigmentation, permanent loss of hair, excessive dryness of skin, excessive longitudinal ridging of nails, keratosis and skin carcinomas.

INTRODUCTION

Radiotherapy is a common modality in cancer treatment and more than 50 % of affected patients will eventually receive some form of radiotherapy as definite, preoperative, postoperative or palliative treatment.[1]

Radiotherapy can result in common, inevitable cutaneous side effects, such as, acute and chronic radiodermatitis[2] and systemic side effects.[3]

Radiation induced skin changes were recognized soon after the discovery of x-rays and were scientifically reported as early as 1902. Even when the skin is not the primary target, it may be injured as an "innocent bystander" and develop profound alterations on functional, gross, and molecular levels.[4]

Acute radiation effect is defined as changes occurring within 2 to 3 weeks of starting radiation and continuing 3 to 4 weeks after completion of therapy. [5]

Acute radiation dermatitis manifests as erythema, edema, burning or tingling, pruritus, pigmentation, desquamation, epilation, shedding of nails, vesiculation or bulla formation, erosion or ulceration. Chronic changes may not develop

for months to years after exposure.[4] Chronic radiation changes include excessive wrinkling or atrophy of the skin, hyperpigmentation, permanent loss of hair, excessive dryness of skin, excessive longitudinal ridging of nails, keratosis and skin carcinomas.[6]

Historical background

Radium therapy began with the famous "Becquerel burn." It was in 1901 that Becquerrel placed a tube of radium in the pocket of his waistcoat, where it remained for several hours. A week or two afterward, a severe inflammation appeared on the skin.[7]It was not long before the physiological effects of radiation were noticed. In April 1896, Daniel described epilation and a serious skin reaction after prolonged exposures; other reports soon followed, the realization that the large doses of x-rays produced harmful effects on the skin suggested that beneficial effects on skin diseases might be obtained with lower doses. In1896, Freund of Vienna observed epilation by x-rays therapy of a large hairy nevus and followed this by treating various inflammatory diseases, including eczema, psoriasis and ringworm, with x-rays.[7]

Biological effects of radiation

Biochemical effects: It seems apparent that radiation causes some changes in the individual molecules like water, proteins, amino acid, sulfhydryl compounds, nucleic acids, enzymes etc. of cells.

Cellular effects: inhibit mitosis; increases cell permeability.

Somatic effects: somatic cells have varying degree of sensitivity towards radiation with hematopoietic cells being the most sensitive and neuromuscular being the least.

Genetic effects: Induces mutation that are transmitted to future generations.[7, 8, 9]

Radiobiology of skin and hair

Within 2 to 3 weeks after exposure of human skin to high doses of fractionated radiation, acute erythema, moist desquamation, erosions, and epilation occur, followed by healing. The intensity of radiation, erythema depends on age, gender, anatomic site, dose and dose rate. These early changes reflect injury, apoptosis and reproductive failure in germinative epidermal and hair matrix cells, reduced division rates in surviving cells, and vascular damage. Epidermal cell replacement occurs from third to the fifth week after radiation. Later chronic post radiation changes result largely from injury to dermal structures particularly the vasculature and fibrosis, which is actually an early (within 1 week) but progressive post radiation events that is cytokine mediated.[10]

The character and magnitude of cutaneous response to radiation depends on total dose and dose fractionation, radiation quality and ionization density, area or volume of tissue irradiated, anatomic site and vascular response. 3 Gy produces complete, reversible anagen alopecia; permanent alopecia begins to occur at 5 Gy.[10]

Radiobiologic effects on melanocytes and pigment formation

Low dose radiation induces cutaneous hyperpigmentation after minimal inflammation. Pigmentation is directly related to dose rate and total dose, and is characterized by increased numbers of melanocytes with increased tyrosinase activity, and by enhanced melanin transfer to epidermal cells. Higher radiation doses destroy melanocytes with resultant depigmentation. Similar radiation effects occur in mid anagen hair follicles. At higher dose rates, hair melanocytes are far more susceptible to radiation destruction than epidermal melanocytes. [10]

Permeability barrier function of skin exposed to ionizing radiation

Radiation induced skin changes appear to be due to impairment of epidermal permeability barrier function, since these changes are associated with an increase in transepidermal water loss (TEWL) and preservation of the barrier function by topical treatment has been found to ameliorate radiation dermatitis.[11]

The functional damage to the stratum corneum induced by the ionizing radiation occurs with a delayed course, starting within a mean period of 11 days and reaching maximal values after a mean period of 27 days (range, 13-75 days). The onset of TEWL increase precedes the onset of radiation dermatitis and the maximal TEWL measurements precede the peak of skin changes. Patients with an early onset of TEWL increase show a longer duration of skin symptoms.[11]

Classification of Cutaneous effects of radiotherapy

Acute radiation dermatitis

Chronic radiation dermatitis

Radiation recall dermatitis

Eosinophilic, polymorphic, and pruritic eruption of radiotherapy (EPPER)

Radiation induced dermatoses

Risk factors

Risk factors associated with cutaneous effects of radiations are broadly divided in to two types: treatment-related factors and patient-related factors. Treatment related factors includes large treatment field, Specific susceptible treatment fields {e.g., thin epidermis (face, neck), bony prominence (clavicle), body folds (ear lobe, pinna, nose),Incision line or wound, peristomal skin},treatment with electron-beam therapy, treatment with tangential fields, radiation given postoperatively, and radiation given after or concurrently with chemotherapy. Patient-related factors are poor nutritional status, fair complexion, history of severe skin reactions to sun exposure, diabetes, preexisting connective tissue or autoimmune diseases(scleroderma, systemic lupus erythematosus and rheumatoid arthritis), infectious diseases (human immunodeficiency virus) ,and others (burned skin, skin donor sites, etc) [4, 5]

Acute radiation dermatitis

Acute radiation effect is defined as changes occurring within 2 to 3 weeks of starting radiation and continuing 3 to 4 weeks after completion of therapy. [5] Acute radiation dermatitis manifests as erythema, edema, burning or tingling, pruritus, pigmentation, dry desquamation, moist desquamation, epilation, shedding of nails, vesiculation or bulla formation, and erosion.[6]

Classification of acute radiation dermatitis [4]

Grade 0 – None

Grade 1 – Faint erythema or dry desquamation

Grade 2 – Moderate to brisk erythema or patchy moist desquamation, mostly confined to skin folds and creases; moderate edema

Grade 3- Confluent moist desquamation ≥ 1.5 cm diameter not confined to skin folds; pitting edema

Grade 4 – skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion

Roentgen erythema:

The erythematous response to X-ray is composed of early erythema that begins within minutes to 24 hours after irradiation and persist for 2-3 days. The main erythematous phase begins 7-8 days after irradiation. The erythema deepens and increases over the next 7-8 days. Hyperpigmentation is noted as the main erythematous phase abates, approximately 4 weeks after irradiation. Occasionally, a third delayed erythematous response occurs 6-7 weeks after irradiation. The response lasts 2-3 weeks but may be obscured by coexisting hyperpigmentation. [12]

Histopathology of acute radiation dermatitis:

It consists of marked intra- and extra cellular edema of the epidermis together with liquefaction degeneration of the basal cell layer. Many pyknotic nuclei are evident. Flattening or effacement of the rete ridges sometimes occurs. In the dermis large accumulations of edema fluid occur. Sometimes leading to dermoepidermal separation and the formation of subepidermal bullae. Swelling of the endothelial cells of the blood vessels takes place. The blood vessels themselves are often dilated. Thrombosis and extravasation of red blood cells can be seen. As healing take place, the stratum corneum and granular layer may thicken while the epidermis itself may be somewhat thinned. The dilatation of dermal blood vessels may become permanent, giving rise to telengiectasia. Adnexal structures often undergo atrophy. The dermal collagen may show clumping and fragmentation. [13]

Eosinophilic, polymorphic, and pruritic eruption of radiotherapy (EPPER)

This complication of radiotherapy for cancer, particularly of the cervix, has a unique clinicopathological profile. It has been diagnosed in the past as erythema multiforme and bullous pemphigoid following radiotherapy. The eruption is widespread, polymorphic and intensely pruritic commencing during radiotherapy and lasting several weeks or months. The lesions are usually erythematous papules, measuring 3 to 10 mm in diameter. Wheals, vesicles and tense subepidermal blisters are less common. On histopathology, there is usually spongiosis with focal spongiotic vesiculation. There may be some acanthosis in lesions of longer duration and secondary changes of rubbing and scratching. The dermal infiltrate is usually superficial and deep and of moderate severity. Eosinophils are always present. There is usually some eosinophilic spongiosis; an eosinophilic panniculitis is much less common. [14]

Isolated case reports

There are isolated reports of lichen planus confined to a radiation therapy site [15], radiation

induced Stevens-Johnson syndrome [16], erythema multiforme [17], cutaneous lymphangiectasis [18], Dariers disease [19], bullous pemphigoid [2], discoid lupus erythematosus [20], localized acneiform eruption [21], Sweet's syndrome [22], pemphigus, asteototic eczema, non specific hypersensitivity reaction including urticaria, delayed breast cellulitis. [4]

Complication of acute radiation dermatitis

The most common and most annoying complication of exudative or ulcerative radiodermatitis is secondary bacterial infections. Impetigo and other pyodermas may occur as well as infectious eczematoid dermatitis. The first indication of latter is redness and swelling, with itching and burning or stinging, beyond the confines of previous inflammation. The dermatitis soon becomes exudative, spreads by peripheral extension, and may become generalized unless checked by antibiotic agents. In some patients these uncontrolled pyogenic infections may result in severe systemic illness. [7]

Occasionally, in acute reactions of second and third degrees, and even in those of first degree, there is considerable deep-seated edema of the unexposed adjacent tissue. This is especially likely to occur if the radiodermatitis is in the vicinity of the eyelids. [7]

Chronic Radiodermatitis

The skin may appear relatively normal for a varying duration after radiotherapy, and chronic changes may not develop for months to years after exposure.[4] Sequelae of cutaneous radiation injuries produce changes which are disfiguring and often dangerous. The clinical picture known as chronic radiodermatitis is characterized by atrophy, partial or complete destruction of cutaneous appendages, telangiectasis, sclerosis of underlying tissue, pigmentary changes, ulceration, alopecia, dystrophy of the nails, keratoses and various premalignant and malignant neoplasms. [7]

Certain of these may appear concomitantly with the acute reaction, or follow it immediately. In many instance their occurrence may be delayed for one or more years; some may not have their onset until fifteen to twenty years after exposure. [7]

Characteristic and frequently seen, are the late changes occurring, usually on the hands, in individuals who have been exposed to x-rays or radium over long periods of time. It is not uncommon to see all the phenomena described above in professional groups such as physicians, particularly those engaged in fluoroscopy, or among x-ray or radium technicians, physicists and veterinarians, as the result of occupational exposure. [7]

Atrophy: cutaneous atrophy is an exceedingly frequent sequel. It usually follows second degree and third degree reactions, but may occur after mild reactions of the first degree. The most common atrophic manifestation is wrinkling. After severe reactions, the skin may be thin, shiny, dry, scaly, semi translucent and wrinkled-resemble parchment. Another type of atrophy is the "hidebound skin," which is attached to dense and sclerotic underlying tissues-resemble scleroderma. [7]

Telangiectasia: telangiectasia is seen most commonly after second degree and third degree reactions, which is usually of radiating type.

Telangiectasia may disappear spontaneously in the course of time, but usually it is permanent. [7]

Sclerosis: injuries of the subcutaneous tissues may result in destructive changes leading to a progressive induration of the connective tissue. If areas about the joints are involved, partial or complete ankylosis may result. This occurs frequently with radiation injuries on the hands. [7]

Pigmentation: may appear without antecedent erythema, often after but a small exposure to radiation, especially following grenz-ray therapy. As a rule it will fade within a few weeks, but it may persist for several months or even a year or more. [7]

Appendages: Radiation can reduce or even destroy the hair follicles, sweat gland and sebaceous gland activity. [7]

Mucous membranes: similar to that of skin. [7]

Nails: severe, acute radiation injury of the distal end of a finger may result in a temporary or permanent defluvium of the nails. As a rule, regrowth occurs. More common are the late nail manifestations such as transverse or longitudinal ridging, discoloration, slow growth, brittleness, and secondary paronychial infections. [7]

Ulcers: develop in any area in which there is severe and extensive radiodermatitis, but the dorsa of the hands are more ulcer-prone than are other parts of the body. [7]

Keratoses: common after reactions of the second and third degree are usually associated with other late findings such as atrophy, sclerosis, pigmentation and telangiectasia. [7]

Cancers: In the literature, the following malignant skin tumors are described as radiation induced: basal cell carcinomas, squamous cell carcinomas, and, in rare cases, sebaceous and sweat gland carcinomas; malignant melanoma; and sarcomas with basal cell carcinoma being the commonest. [7]

Radiation recall dermatitis (RRD)

RRD is defined as a skin reaction, with all the clinical signs of inflammation, in a previously irradiated field subsequent to drug administration (usually cytotoxic drugs) days to years after exposure to ionizing radiation. [23]

Drugs reported as trigger include actinomycin-D [24], tamoxifen [25], interferon alfa-2b [26], simvastatin [27], and antituberculous drugs.[28] Onset is faster with intravenous drugs (ranging from a few minutes to severals days; median, 3 days) than with oral drugs (ranging from 3 days up to 2 months; median, 8 days) . Camidge and Price have proposed that skin reactions brought about by drugs given less than 7 days after radiotherapy should be considered radiosensitization rather than RRD.[23]

Recall reactions are mainly seen in the skin. Other sites reported include the lungs, vaginal mucosa, laryngeal mucosa, central nervous system, bowel, and esophagus. Clinical signs include erythema, desquamation, edema, urticaria-like lesions, vesiculation, necrosis, ulceration, and hemorrhage. Patients usually complain of pruritus and pain. [23]

Grading system for RRD [29]

Grade 1 (mild) -Erythema ± pruritus ± dry desquamation

Grade 2 (mild/moderate) – Grade 1+ pain, edema, urticaria like, vesiculation

Grade 3 (moderate) – Moist desquamation

Grade 4 (severe) – Necrosis, ulceration, or hemorrhage

RRD tends to resolve without specific treatment. Steroids, systemic or topical, and antihistamines control pruritus and/ or pain, but the time of resolution of cutaneous manifestations remains the same with or without steroid or antihistamine treatment. [23]

Treatment of radiation dermatitis [4,30,31,32,33,34,35]

Acute radiation dermatitis

Erythema and dry desquamation are best treated symptomatically with gentle cleansing, emollients (lotions, creams, or ointments), avoiding (friction, UV radiation, temperature extremes, and trauma), and with topical steroids. In addition to this, moist desquamation during radiation therapy is treated with hydrogel dressings, Hydrocolloid dressings for minimally exudative wounds, Burns pads, alginate, or foam dressings for highly exudative wounds and to treat infected wounds topically or systemically based on results of bacterial culture. Moist desquamation after radiotherapy is manage as above with the addition of film dressing for minimally exudative erosions, and infected wounds with Ionic silver pads or powder, topical antibiotics, cadexomer iodine, maltodextrin powder.

Chronic radiation dermatitis

Therapeutic strategies to ameliorate ulcers of chronic radiation dermatitis include

careful and selective ulcer debridement (mechanical, enzymatic, autolytic, and biosurgical), recombinant PDGF, biologic preparations (growth factors) ,low intensity helium laser, and hyperbaric oxygen. Telangiectasia is treated with vascular laser and the fibrosis of chronic radiation dermatitis is manage with Pentoxifylline, Pentoxifylline + Vitamin E, interferon Gamma and with superoxide dismutase

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