

Review Article

Radiation-recall dermatitis associated with cytotoxic chemotherapy

化療有關的放射線回應性皮炎

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Radiation-recall dermatitis is a well-recognised phenomenon of an acute inflammatory toxicity that occurs in a previously quiescent radiation field with subsequent cytotoxic chemotherapy administration. It may occur from days to weeks, and sometimes years after the radiation therapy. The precise mechanism is unknown. One hypothesis suggests that the initial radiation therapy leads to a depletion of tissue stem cells within the irradiated field and that subsequent cytotoxic chemotherapy exposure causes a 'remembered' reaction among the remaining surviving cells. An alternative proposition suggests that radiation induces heritable mutations within surviving cells which then produce a subgroup of defective stem cells that are unable to tolerate the second insult of chemotherapy. Treatment is mainly supportive and most of the lesions will heal spontaneously. Some reports have noted that radiation recall dermatitis recurred with subsequent continual administration of the same chemotherapeutic agent, however such experience is non-universal. Preventative measures that have been employed to avoid recurrence of the condition include subsequent cytotoxic dose modification, prophylactic steroid coverage, and discontinuation of the implicated cytotoxic.

放射線回應性皮炎是為人熟知的現象。在過往曾經接受放療的無症狀區域，於化療後即出現急性炎症反應。它可於放療後數天，數週甚至數年出現。其確切的發病機制尚未明瞭。其中一個假設是，早期的放射治療令組織中的幹細胞減少，其後的化療則令餘下的幹細胞產生“回憶反應”。另一個假設是，早期的放療令餘下存活的細胞產生可遺傳的突變缺陷，而這些帶缺陷的幹細胞群落不能耐受其後的化療。此症主要用支持療法處理，皮損通常自行痊癒。病例報告中也有些放射線回應性皮炎再接受相同化療藥物後復發，但這並非會必然發生。預防措施包括：調整化療劑量，並用皮質激素以及停用懷疑致病的化療藥。

Keywords: Cytotoxic chemotherapy, radiation-recall dermatitis

關鍵詞：化療，放射線回應性皮炎

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Introduction

Radiation therapy on the skin may lead to acute or chronic radiation dermatitis, radiation-recall dermatitis or secondary malignancy. Acute radiodermatitis usually occurs in patients undergoing radical radiotherapy such as post-operative chest wall irradiation for breast cancer,

where the reaction becomes apparent around day 14 of a four-week course of treatment. Epilation occurs in the initial stage, followed by erythema, which is accompanied by warmth and oedema over the irradiated skin. The skin may become pruritic and pigmented. Dry and occasionally wet desquamation may become evident. The regeneration of new skin occurs about a week after the completion of radiotherapy and recovery is usually complete within three weeks of finishing treatment. In chronic radiodermatitis, by contrast, the skin reaction may be permanent. Ischaemia, pigmentation of varying degrees, thickening due to fibrosis, telangiectasia and late ulceration may occur. Radiation-recall dermatitis is the occurrence, with subsequent chemotherapy administration, of an acute inflammatory toxicity in a previously quiescent radiation field. Apart from reactivation in the skin, the buccal mucosa, lungs, oesophagus and other intestinal epithelium, heart and bladder mucosa may also be involved.¹⁻⁵ Radiation-recall has also been thought to be a delayed form of radiosensitisation.⁵ As a consequence, while it is generally considered as an unwanted side effect, it may be useful in the potentiation of radiation therapy when concurrent chemo-radiation is applied.

Associated agents

There are a number of agents that have been reported to cause radiation recall phenomena (Table 1). These include the anti-neoplastic antibiotics (actinomycin, doxorubicin, daunorubicin, bleomycin), cytarabine, lomustine, cyclophosphamide, fluorouracil, hydroxyurea, mercaptopurine, methotrexate, trimethotrexate, vinblastine, melphalan, etoposide and tamoxifen.⁶⁻¹⁴ More recently, newer cytotoxic agents including the taxanes (paclitaxel and docetaxel),^{15,16} oxaliplatin,¹⁷ gemcitabine,¹⁸ capecitabine,¹⁹ and interferon alfa-2b²⁰ have also been reported to be associated with radiation therapy recall reactions. Furthermore, steroid

withdrawal has also been reported to activate latent radiation injury to the heart and lungs.^{1,4}

Prevalence

The prevalence of radiation recall dermatitis differs between chemotherapeutic agents. Apart from the anti-neoplastic antibiotics, most information on other agents has been based on isolated case reports. For dactinomycin, Tan et al²¹ reported that of a total of 57 patients who had irradiation prior to dactinomycin therapy, 27 (47%) developed

Table 1. Agents that have been reported to be associated with radiation recall reactions

Antineoplastic antibiotics

Bleomycin
Dactinomycin
Daunorubicin
Doxorubicin

Taxanes

Docetaxel
Paclitaxel

Antimetabolites

Cytarabine
Flourouracil
Mercaptopurine
Methotrexate
Trimetrexate

Alkylating agents

Cyclophosphamide
Melphalan

Vinca alkaloids

Etoposide
Vinblastine

Others

Hydroxycarbamide
Lomustine
Tamoxifen
Capecitabine
Oxaliplatin
Gemcitabine
Interferon alfa-2b

cutaneous reactions over the previously irradiated areas.

With newer agents like the taxanes, for a group of patients who had prior radiotherapy, subsequent administration of docetaxel (eight as single agent therapy, 24 as combination therapy with an anthracycline) resulted in two out of 32 patients (6%) developing radiation recall dermatitis over previous irradiated areas;¹⁶ however, the possible role of epirubicin in the recall reaction in one of these cases could not be totally excluded.

Clinical and histological features

The clinical features are described with the patient illustrated in Figure 1. This patient was treated with radiotherapy for his nasopharyngeal carcinoma two years ago. He presented with metastatic lung disease and was treated with paclitaxel-carboplatin combination chemotherapy (which required dexamethasone as part of the standard pre-medication). A few days after the first dose of cytotoxic treatment, a skin rash appeared over the neck. This was managed as cellulitis with antibiotics, after which the lesion resolved. After the second cycle of chemotherapy, there was reappearance of the skin rash over the neck region. The lesion was well-demarcated, erythematous and occurred over both sides of the neck with sparing of the midline region; the patient also developed mucositis and laryngitis with laryngeal oedema that required tracheostomy.

Apart from the usual results of radiation-chemotherapy interactions on the skin such as erythema followed by dry desquamation (Figure 1), there may be associated painful vesicles and oozing, in the most severe of cases, necrosis and persistent painful ulcerations.

Biopsies from the affected skin showed epidermal dysplasia, keratinocytes with features of necrosis, increased mitotic figures, and a mixed inflammatory infiltrate; and in some cases, psoriasiform dermatitis with clearing within cells in the upper layers of the epidermis have been observed. Additional dermal changes included dermal fibrosis, vasodilatation, and atypical fibroblasts. Moderate to marked solar elastosis could be seen. Further, there appeared to have increased p53 immunohistochemical staining in the affected skin when compared with areas that have not been irradiated.²²

Time interval from radiation

Radiation-recall dermatitis may occur from days to weeks and sometimes years after the radiation therapy. The skin reaction may or may not be preceded by clinically apparent radiation damage in the involved organ. In patients who received anthracyclines after radiation therapy, most cases of recall dermatitis have developed four to seven days after the injection of the drug and within four months of the radiation therapy;



Figure 1. Well-demarcated erythema as a result of radiation-recall dermatitis over previous radiotherapy field in the neck area.

the recall dermatitis may last for up to seven days. However, the skin reaction may develop up to 17 months after radiation therapy when the drug is given.⁶

D'Angio et al⁷ observed that the severity of the reaction was greatest when the interval between radiation therapy and chemotherapy was shortest. In animal studies, radiation-recall pneumonitis was more severe among animals given doxorubicin within two months than at three months after lung irradiation.²²

Studies have suggested that different drug and dose-timing combinations may influence the onset of radiation recall dermatitis. In a case study reported by the author, the radiation recall dermatitis occurred not with the first dose of docetaxel, but after a second dose of the cytotoxic, which was 49 days after radiation, and a 'threshold' radiation dose for the recall reaction was reported to be between 16.8 and 18.7 Gy.¹⁶ While in a case of Kaposi sarcoma treated with radiotherapy,⁸ recall dermatitis with a second dose of bleomycin occurred 15 days later in an area that was being treated to 40 Gy; there was no reaction in the other areas that were treated with 20 or 8 Gy. Similarly, Sears described recall dermatitis in two treated fields in the same patient who received hydroxyurea, one occurring in a field given 30 Gy with a 44-day interval compared to the other with a field given 16 Gy with a 20-day interval.¹³

Interactions between radiation and cytotoxic agents

Enhanced radiation injury by cytotoxic agents has been seen following even low doses of radiation (12 to 26 Gy).²² Three types of interactions between the chemotherapeutic agent, the tissue irradiated and the effect of radiotherapy that is enhanced have been described by Phillips and Fu.²² In the first type,

broad-spectrum radiosensitisers such as the anti-neoplastic antibiotics, in particular, doxorubicin and dactinomycin appear to affect any tissue irradiated. The second type of interaction involves chemotherapeutic agents that tend to be tissue specific in their toxic effects, e.g. bleomycin which is toxic to the lungs, cyclophosphamide which is toxic to the bladder mucosa and doxorubicin which is a broad-spectrum sensitizer that is especially toxic to the heart and skin. Radiation to these tissues enhances the known toxic effect of the agent on the tissue. These two types of interactions can be predicted to a certain extent. The third type of interaction may involve any of the types of chemotherapy agents where radiation injury is enhanced without any evidence of a toxic effect when the drug is used alone. This interaction seems to be much less common and is more difficult to predict. These three types of interactions can be observed when the drug is given concurrently or subsequently after irradiation as a recall phenomenon.

Possible mechanisms

The precise mechanism of radiation-recall dermatitis remains unknown. Most of the drugs involved are DNA-intercalating agents such as the anti-neoplastic antibiotics, which disrupt the DNA molecule, and also trigger the formation of free radicals. Radiation also cleaves DNA and renders it vulnerable to free radical attack. One possible mechanism is that these agents inhibit cellular recovery after radiation exposure via inhibition of DNA repair.²² Agents like paclitaxel act by stabilising microtubules and hence selectively blocks cells in the most radio-sensitive phase of the cell cycle (G2/M). Recent in vitro studies using cell lines have shown that taxanes may be acting as cell cycle selective radiosensitisers, but it is unclear how this action correlates with an ability to reactivate latent radiation effects in normal tissues.²³

It has been suggested that the initial radiation therapy leads to a depletion of tissue stem cells within the irradiated field and that subsequent cytotoxic exposure causes a 'remembered' reaction among the remaining surviving cells.

An alternative proposition has been supported by a study from Seymour et al²⁴ in which, after a dose of radiation, lethal mutations were produced among surviving cells, which then produce a subgroup of defective stem cells that are unable to tolerate the second insult of chemotherapy. They proposed that surviving cells could pass the lethal defects along to their descendants. Further, even though a tissue would appear to be fully reconstituted after a course of radiation therapy, a significant proportion of stem cells would be incapable of further proliferation leading to an enhanced response to the second therapy.²⁵ However, work by Kitani et al²⁵ appeared to have disproved this theory. By using irradiation at different dose rates, they demonstrated that sub-effective damage that led to lethal mutations could undergo considerable repair. Finally, while the host immune response has been suggested to be associated with the development of recall reactions, the observation that the latter usually occur at the time when significant immunosuppression exists suggest that such tissue response is not an immune-mediated event.¹¹

Genetic susceptibility

Certain genetic disorders may manifest enhanced radiosensitivity. One of the most interesting inherited diseases in this respect is ataxia telangiectasia (AT). AT carriers have been observed to be more prone to enhanced radiosensitivity,²⁶ and this has been supported by in vitro studies on cell cultures.²⁷ Furthermore, exposure to ionising radiation results in activation of complex signal transduction pathways, which eventually shape the response of cells. Some of the important pathway responses include the transcription factor p53

pathway, MAP kinase (MAPK) cascades and nuclear transcription factor- κ B (NF- κ B) activation, as well as signaling events initiated at the cell membrane and within the cytoplasm. Alterations on gene expression play roles both as intermediaries in signaling and downstream effector genes. Differences in cell type, interindividual genetic differences and crosstalk occurring between signaling pathways may help to channel radiation stress signals between cell cycle delay, enhance DNA repair, and apoptosis. These differences may in turn help determine likelihood of late effects of radiation exposure.²⁸

Management

Most radiation recall dermatitis will resolve spontaneously without specific treatment. However, as in one report of recall supraglottitis, the administration of corticosteroid may be life saving.²⁹

In most cases of radiation recall dermatitis, the affected patients were not rechallenged with the same implicated drug. To date, apart from the patient illustrated in Figure 1, 15 other patients have been reported to be rechallenged with the same implicated drug for the recall dermatitis.³⁰ Of the 16 patients, 11 showed recurrence of the skin reaction (with four having milder reactions). Of these, five were rechallenged with a further dose, and three showed recurrence of the reaction. In the five cases successfully rechallenged without recurrence of the recall dermatitis, three received treatment modifications prior to receiving the same cytotoxic, that is, either a dose reduction (in one), or the use of prophylactic steroid cover (in one), or both (in the remaining one). For those who had recurring lesions upon rechallenging, only one patient (Figure 1) received steroid cover (as part of the pre-medication for paclitaxel); treatment modifications were not adopted in the others. However, it is noteworthy that for those who did not have the recurrence of the reaction

(two patients on the first rechallenge and two on the second rechallenge), neither of the prophylactic measures was employed. Thus, the role of these prophylactic measures remains unclear. Based on these data, there is as yet no means of predicting an individual's risk of developing recall dermatitis in terms of a drug dose threshold or a specific time period after radiotherapy when the chemotherapeutic agent is administered.

Conclusion

With the wider application of radiotherapy and chemotherapy in treating malignant disease, familiarity with radiation recall reactions and their potential complications may expedite early diagnosis and appropriate management. The drug and time-dose relationship that bring about the radiation recall reactions remains unclear. Thus, the decision as to whether a specific chemotherapeutic agent should be continued after the occurrence of radiation recall dermatitis will depend on a number of factors. Having taken into account the availability of alternative therapy, these include individual patient wishes in continuing an effective anti-tumour treatment, the clinical judgment as to the potential risk (severity of the recall reaction) and the possible benefit gained (in terms of drug efficacy in tumour control) from continuing the same treatment.

Genetic studies using the tools of the postgenomic era will enable high throughput studies of the multiple changes resulting from the interplay of radiation signaling pathways. Gene expression profiling, in particular, shows great promise, both in terms of insight into basic molecular mechanisms and for the future hope of biomarker development and individual tailoring of cancer therapy.

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