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# Isodose 20 Gy found as a threshold dose for radiation recall dermatitis

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ABSTRACT

Radiation recall is a rare phenomenon that can be observed in the field of radiotherapy, months or years after irradiation when a patient is exposed to certain pharmaceutical agents. In this report, we relate a case of radiation recall dermatitis induced after the application of a topical natural cream, 2 years after the initial radiotherapy treatment. Skin reactions were severe and limited to the irradiated volume, whereas a large part of the skin where the cream was applied outside the radiation field was strictly normal. More precisely, the radiation recall dermatitis matched with the isodose 20 Gy, whereas no recall reaction was observed in the lower dose areas (5, 10 or 15 Gy) despite these areas were also largely exposed to the cream. **In conclusion**, this is the first report that could provide a threshold dose for the occurrence of a radiation recall dermatitis, which was not observed below 20 Gy, in the context of this topical reagent.


## 1. Introduction

Radiation recall phenomenon is an acute inflammatory reaction within a previously quiescent radiation field (the skin and other sites) after the administration of various pharmacological agents. It was first described with some chemotherapy agents but it can also been observed with antibiotics [1,2], tamoxifen [3,4], statins [5,6], and exposure to ultraviolet light [7,8]. Although the radiation recall phenomenon is always observed in the irradiated volume [9–11], it is not known what dose level of irradiation in tissue can be associated with this phenomenon. We report a case of RRDradiation recall dermatitis (RRD) triggered by a topical cream, with skin reactions restricted to the 20 Gy isodose and above.

## 2. Case report

In 2014, a 54-year-old man presented with a squamous-cell carcinoma of the tonsil T2 N2 M0. His previous medical history included ethyl cirrhosis child B. Given a presentation of locally advanced oropharyngeal cancer, he was treated by concomitant cetuximab and radiation therapy (6 MV photons, TomoTherapy, Accuray®): 69.96 Gy in 33 fractions of 2.12 Gy on tumor and involved nodes on right neck. Elective nodal irradiation consisted of 52.8 Gy in 33 fractions of 1.60 Gy from Ib to VI lymph node areas. According to CTCAE v4, grade 1 acute toxicity (erythema skin reaction) and grade 1 late toxicity (bilateral neck fibrosis) were observed. Two years after the treatment, he had a relapse in the lower left neck with a lymph node recurrence in level IV. Two weeks after this diagnosis, the patient had a mild muscle pain in his left shoulder after doing sports, and he applied a cream bought in a pharmacy on his left cervical supra clavicular area. This cream was a topical cream infused with essential oils and natural plants extracts (Fig. 2). The surface of application of the cream on the skin was the entire left shoulder, the lateral left neck and all the areas in between.

Two days after the application of the cream, the patient reported skin symptoms characterized by a marked discomfort sensation in the skin with a redness on his left neck. One day after, the patient was seen in our clinic and a deep purple redness, marked discomfort, swelling, and tingling of the left neck were observed. Toxicity was scored as grade 2 erythema (according to CTCAE v4), grade 1 purpura with local dilatation of small vessels resulting in red discoloration of the skin (telangiectasia grade 1). There was no rash, no vesicle, no skin induration, or ulceration. Four days after the application of the cream, a marked increase of the symptoms was observed with grade 2 skin pain, grade 2 telangiectasia, and grade 2 erythema (Fig. 1a). These reactions were interpreted as a recall phenomenon, since the skin reactions were limited to the intersection between the application of the cream and the previously irradiated volume, whereas a large part of the skin where the cream had been applied outside the radiation field was strictly normal (Fig. 1a). When matching the skin

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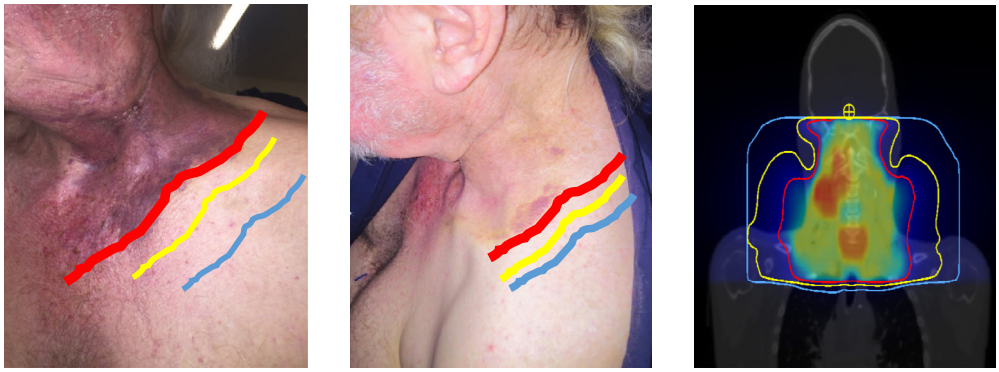


**Fig. 1.** Evolution of the skin reaction and their matched with previous isodoses. Skin reaction at day 4 (a), skin reaction at day 15 (b) and coronal view of dosimetry showing radiation isodose 20 Gy (red), 10 Gy (yellow) and 5 Gy (blue) (c). The Deep Blue® cream was applied both inside and outside the radiation field (on the left neck and on the shoulder). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Aqua, Gaultheria procumbens (Wintergreen) Leaf Oil, Cinnamomum camphora (Camphor) Bark Oil, Menthol, Cetearyl Alcohol, Prunus amygdalus dulcis (Sweet Almond) Oil, Stearic Acid, Glyceryl Stearate, PEG-100 Stearate, Mentha piperita (Peppermint) Oil, Eucalyptus globulus (Eucalyptus) Leaf Oil, Caprylic/Capric Triglyceride, Butylene Glycol, Capsicum frutescens Extract, Chamomilla recutita (Blue Chamomile) Flower Oil , Tanacetum annuum (Blue Tansy) Flower Oil, Helichrysum italicum (Helichrysum) Flower Oil, Allantoin, Gardenia florida Fruit Extract, Osmanthus fragrans (Osmanthus) Flower Extract, Aloe barbadensis Leaf Juice, Chlorella vulgaris Extract, Retinyl Palmitate, Squalane, Ceteareth-20, Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer, Dimethicone, Phenoxyethanol, Caprylyl Glycol, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Xanthan Gum, Ethylhexylglycerin, Hexylene Glycol, Polysorbate 60, Maltodextrin, Sodium PCA, Tetrasodium Glutamate Diacetate

**Fig. 2.** Ingredients of Deep Blue® cream.

reactions with the irradiation isodoses, the reactions were restricted to the region having received 20 Gy and more, whereas the region where the cream has been applied but having received less than 20 Gy exhibited no reactions (Fig. 1c). Nine days after, a marked decrease of skin reactions was observed without any therapeutic intervention with erythema grade 1, no more pain, no telangiectasia, and no oedema. On day 15, the skin almost returned to normal (Fig. 1b).

## 3. Discussion

The ability of certain pharmaceutical agents to elicit inflammatory reactions in previously irradiated areas, several years after the initial effects of the radiation has been recognized more than 40 years ago. Our case provided an opportunity to observe a RRD only in a well-defined area, and appeared to be dependent on radiation dose, matching with the 20 Gy isodose.

This is the first report suggesting a strong correlation with a threshold dose of irradiation, which could not be found in previous reports since the majority of them specified the radiation dose to the tumor, rather than to the area where the RRD was observed. The tumor dose ranged from 10 to 61.2 Gy [12]. For only two cases report, a threshold dose was suggested. Yeo et al. [13] found that docetaxel induced RRD occurred only in skin receiving 18.7 Gy or 21.5 Gy, but not at 8.7 Gy or 16.8 Gy which is consistent with our observation. However, Stelzer et al. [14] reported a RRD triggered by bleomycin occurring at a possible higher threshold dose of 40 Gy.

A number of different hypotheses have been proposed to explain RRD, although with little evidence base to support any of them. Essentially, the hypotheses focused on either vascular, epithelial stem cell, epithelial stem cell sensitivity, or drug hypersensitivity reactions as the mechanism for RRD. Given the composition of the cream, including more than 35 products (Fig. 2), it was very difficult to identify which of them was (were) responsible for the recall phenomenon observed in our patient. It is also not known if the threshold dose is a phenomenon essentially observed with topical applications, as it is the case in our patient.

Finally, a wide range of drugs has been associated with RRD. Recently, some reports of radiation recall reactions after molecular targeted therapies have emerged. These targeted therapy are drugs that interfere with cell growth signalling, tumour blood vessel development and stimulate the immune system. A few case reports have emphasised that drugs targeting EGFR pathway may cause RRD. This, include a case report of RRD triggered by a topical natural cream, following concurrent therapy with radiation and cetuximab, a monoclonal antibody that binds to the extracellular domain of epidermal growth factor receptor (EGFR). Blockade of EGFR signaling sensitizes cells to the effects of radiation. A number of different hypotheses have been proposed to explain RRD, although with little evidence base to support any of them. Changes in the local immune environment and the response of stem cells to inflammatory signals have been described after exposure to ionizing radiation. It is therefore plausible that radiotherapy associated with cetuximab may have the ability to lower the local threshold at which potentially systemic reactions may become manifest. Thus, it is not possible to rull out that the initial Cetuximab-RT combination might influence the threshold dose associated with this phenomenon.

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