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CASE REPORT

An illustrated case of doxorubicin-induced radiation recall dermatitis and a review of the literature

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ABSTRACT

Radiation recall dermatitis (RRD) is a rare cutaneous reaction occurring within a previously irradiated field, precipitated by certain drugs. A case of RRD most likely induced by doxorubicin is presented and illustrated together with a review of the literature.

KEYWORDS

Recall dermatitis, radiotherapy, doxorubicin

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

Radiation recall dermatitis (RRD) is defined as the appearance of skin reactions in previously irradiated skin after the administration of certain response-inducing drugs. The incidence of RRD is poorly documented but generally this condition is regarded as rare. The first published case, by D'Angio and colleagues in 1962,[1] was triggered by dactinomycin. Some medications have been documented to be more commonly associated with RRD, such as doxorubicin, gemcitabine, and docetaxel. Here we present a case of RRD most likely induced by doxorubicin.

CASE REPORT

Patient and tumour characteristics and radiotherapy regimen

A 44-year-old female patient was treated for breast cancer. She was not taking any medication or alcohol; she smoked 10 to 15 cigarettes daily. Her medical history revealed episodes of eczema for many years for which she had frequently used topical corticosteroids. Slight atrophy of the skin as a result of this was predominantly seen on her hands, but not on her breast. The tumour was a 2.2 cm large grade III infiltrating ductal carcinoma, the receptors for oestrogen and progesterone were both positive, HER2/neu was negative. Axillary dissection showed ten nodes, six of these were invaded by metastases. The axillary apex node was negative. An ultrasound of the liver, a chest X-ray and a bone scintigraphy were normal. Six weeks after breast-conserving surgery, she was irradiated to the left breast, axilla and internal mammary chain, with a boost to the lumpectomy area by a simultaneous integrated boost technique. An elective dose of 50.4 Gy in 28 once-daily fractions of 1.81 Gy was delivered by 6 MV photons without bolus material to the skin by intensity modulated radiotherapy (IMRT) treatment planning. The boost area received 28 fractions of 0.49 Gy by 8 MeV electrons with 0.5 cm bolus material (cumulative dose boost area: 64.4 Gy). She was checked weekly during irradiation and a grade I erythema developed in the 5th week, only to the skin of the axilla but not to the breast.

Exactly 14 days after completion of radiotherapy she started her adjuvant chemotherapy. At the start of chemotherapy, the slight erythema had completely resolved. For personal reasons she decided to photographically document her skin condition prospectively.

Chemotherapy

As adjuvant chemotherapy she received TAC in a three-weekly schedule; taxotere, doxorubicin and cyclophosphamide. A dose of 120 mg docetaxel (Taxotere®), 800 mg cyclophosphamide (Endoxan®) and 80 mg doxorubicin was administered.

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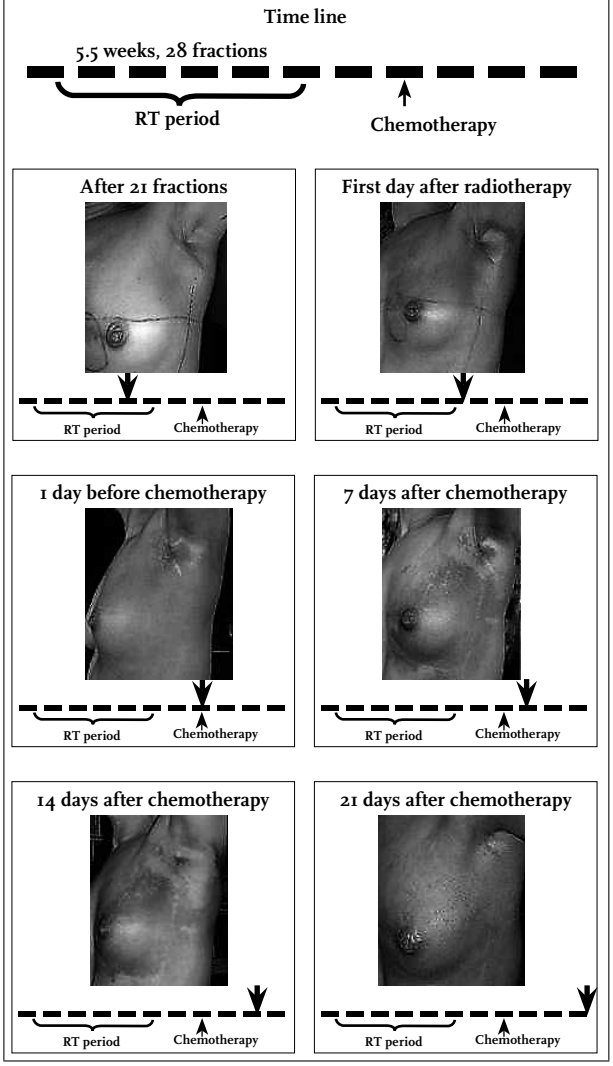
Epicrisis

Two days after the administration of the first TAC course she started to experience a general malaise consisting of feeling cold and shaking. A severe pain developed in the irradiated area. On day 4 after administration of TAC chemotherapy, the irradiated skin started to show an erythema with a purplish aspect. A patchy superficial epidermiolysis developed in the affected skin designated as grade III.[2] The pain subsided after five days, the skin reaction started to recover after 14 days.

Since the indication of adjuvant chemotherapy was considered to be crucial,[3] (adjuvant online), she was encouraged to continue without doxorubicin. On day 22 the second chemotherapy course was administered consisting of TC. The docetaxel dose remained 120 mg, but the cyclophosphamide was escalated to 975 mg. Neither the pain nor the skin reaction reoccurred. Subsequent courses could be administered without reappearance of the recall phenomena. The appearance of the skin over time is depicted in *figure 1*.

Figure 1. *The evolution over time of the skin reaction with respect to the overall treatment time of radiotherapy and the first adjuvant chemotherapy*



DISCUSSION AND REVIEW OF THE LITERATURE

RRD (radiation recall dermatitis) involves the appearance of skin reactions in previously irradiated skin in response to the administration of several drugs, as described in *table 1*. Although the number of published cases is low, there is probably an underscoring of its true incidence. Furthermore, patients need to have had radiotherapy first and therefore this condition is only described in an oncological setting. The severity of the skin reaction is described by the Common Toxicity Criteria version 4.0.[2]

Table 1. *Literature review on drugs probably involved in radiation recall dermatitis*

Drug	References
Doxorubicin and pegylated liposomal doxorubicin	9, 15-18
Docetaxel	6, 19-27
Gemcitabine	20, 28-36
Paclitaxel	37, 38
Methotrexate	39, 40
Tamoxifen	41-44
Dactinomycin	1
Vinblastine	45
Carboplatin	30, 37
Dacarbazine	46
Cetuximab	47
Cyclophosphamide	48, 49
Capecitabine	50-52
Others	Bevacizumab[53], Trastuzumab[54], Pemetrexed[55-57], Gatifloxacin[58], Levofloxacin[59], Lanreotide[60], Gefitinib[61], Arsenic trioxide[62], Interferon alfa-2b[63], Oxaliplatin[64,65], Idarubicin[10], Simvastatin[66], Bleomycin[67]

TEMPORAL RELATIONSHIP BETWEEN USE OF DRUGS AND END OF RADIOTHERAPY

Camidge and Price[4] have further defined the clinical entity and have made a clear separation between radiosensitisation and RDD. They suggest designating any reaction occurring within seven days after administration of drugs as sensitisation and not as RRD. In our case the interval was 14 days and can, by this Camidge definition, therefore be called RDD. Although this interval of two weeks can be considered relatively short, much longer intervals have been described. To the best of our knowledge, the longest reported interval for RDD is seven years by Mayer *et al.*[5] Burdon *et al.* have reported a 15-year interval for adriamycin-induced stomatitis.[6]

PATHOGENESIS

Although the precise mechanism of action for RRD is not known, several mechanisms have been proposed including changes in vascularisation, DNA repair, radiation-impaired epithelial function of stem cells, increased stem cell sensitivity, and increased sensitivity to drugs.[4,7] None of these hypotheses have been proven. Furthermore, the recall phenomena are not only seen in the skin, but also on mucosa and other internal organs.[8-11]

RADIOTHERAPY CHARACTERISTICS

There is no relationship between the occurrence of RDD and the applied radiation dose. Therapeutic schedules well below 20 Gy have been described to elicit RDD as well.[4]
It is a fact that the incidence of radiation-induced skin reactions in the case of breast-conserving therapy predominantly depends on breast volume, beam energy and the use of IMRT.[12] In the patient we have presented the breast was relatively small and she was treated by 6 MV photon IMRT. Based on these characteristics the anticipated chance of moist desquamation was low. Indeed during and in the first two weeks after radiotherapy skin reactions were very mild and desquamation did not occur. The severe adverse effects on the skin were only seen directly after the start of adjuvant chemotherapy. This makes the radiotherapy itself a very unlikely cause of her malaise.

DRUGS ASSOCIATED WITH RRD

Besides chemotherapeutic agents, many more drugs (such as antibiotics, monoclonal antibodies, biological response modifiers) are also able to elicit RRD, but few are administered in close temporal relation to radiotherapy.[13] Several drugs are enumerated in *table 1*.

THERAPEUTIC INTERVENTIONS

There are no proven interventions to relieve symptoms or to enhance recuperation. Once the RDD has occurred almost all reports advise to discontinue the triggering drug. However, a rechallenge does not always result in the occurrence the skin reactions.[4]
Care must be taken when studying the literature on this subject. There are many studies on how to reduce acute radiation skin reactions with creams, amifostine, N-acetylcysteine, etc.[14] But there are no studies on how to manage the skin that was intact after completion of radiotherapy and subsequently developed RDD. Caloglu *et al*. have produced an algorithm on how to manage the recall phenomena.[7] In case of 'severe' reactions they suggest prescribing systemic or topical steroids, nonsteroidal anti-inflammatory agents, and antihistamines. However, the available scoring system[2] subdivides RDD into the usual Grades I to V (there is no 'severe' in the CTC version 4.0) and there is no evidence for these agents.
In conclusion, this case report adds to the already existing knowledge that RRD is a rare though possibly underreported event. To the best of our knowledge, this is the first published case with a prospectively collected series of photographs on the evolution of skin reactions both during the radiotherapy course and the subsequent RDD occurrence and resolution.

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