

Radiation recall dermatitis: report of two cases

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Abstract Systemic treatment for cancer including chemotherapy or biologic agents can cause different changes in the skin or mucous membranes. These changes may represent a known adverse reaction to these drugs, although other etiologies should be considered. One of these, radiation recall dermatitis, is a rare and unpredictable phenomenon. Herein, we report two cases of this condition in women with metastatic breast cancer secondary to gemcitabine and the combination of capecitabine and ixabepilone.

Keywords Recall dermatitis · Breast cancer · Ixabepilone · Capecitabine · Gemcitabine

Introduction

Radiation recall dermatitis (RRD) is a rare inflammatory reaction occurring in a previously irradiated area, precipitated by the administration of certain drugs. It is important to note the difference between the radiosensitization phenomenon with inflammatory changes present during treatment with radiotherapy, versus the recall phenomenon that occurs as a late, unpredictable event. Because of its

rareness and non-specific symptoms, it poses a great diagnostic challenge that requires a high index of suspicion. We describe two cases of RRD secondary to gemcitabine and the combination of capecitabine and ixabepilone, and a short review of literature on the topic.

Case report

Case 1

A 34-year-old woman was diagnosed with metastatic triple negative breast cancer. Her bone scan showed multiple bone lesions and computed tomography (CT) scan showed no visceral disease. She received a 5-fluorouracil (600 mg/m²), doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²)-based chemotherapy for six cycles and then a cleaning mastectomy was performed. After recovery from surgery, paclitaxel plus bisphosphonates were initiated with no toxicity reported.

Six months later, she developed local and systemic progression with subcutaneous nodular lesions in the mastectomy scar and liver metastasis. A skin biopsy was performed which showed diffuse infiltration of tumor cells. She underwent hyperfractionated radiation therapy, using a 6 MV X-ray, to the chest wall at doses of 57, 8 Gray (Gy) in two-daily fractions delivered over 20 days (Fig. 1). The treatment was well-tolerated with only acute erythema followed by signs of re-epithelialization.

Two weeks later, she was offered a new chemotherapy regimen based on capecitabine (at doses of 1250 mg/m² twice daily) plus ixabepilone (40 mg/m²). Three days after completion of chemotherapy she presented to the emergency room with intense pain over the recently irradiated

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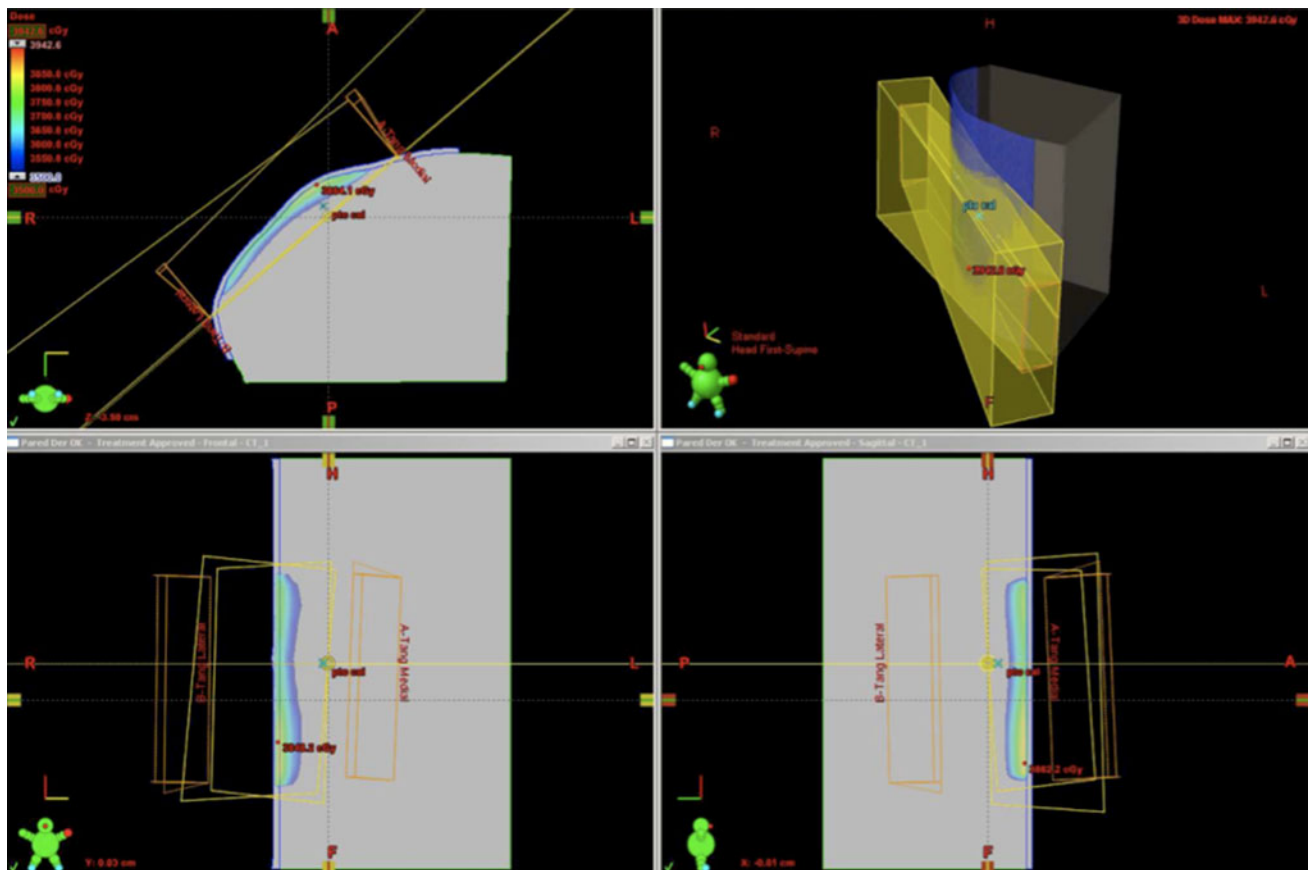


Fig. 1 Radiation planning diagram shows area to be irradiated in a patient with metastatic breast cancer



Fig. 2 **a** Photography showing a well-demarcated zone with intense erythema and vesicles in a previously irradiated area. **b** The same patient, 2 weeks after suspension of chemotherapy and local treatment

chest wall. Physical examination revealed a well-demarcated rectangular area associated with erythema and vesicles (Fig. 2a). The lesions were consistent with the clinical diagnosis of RRD. Chemotherapy was suspended and local treatment with isotonic saline and moisturizing lotion produced an excellent response (Fig. 2b).

Case 2

A 54-year-old woman diagnosed with T1N0, ER positive, HER-2 positive breast cancer was prescribed treatment consisting of a partial mastectomy plus radiation therapy and adjuvant chemotherapy with doxorubicin and

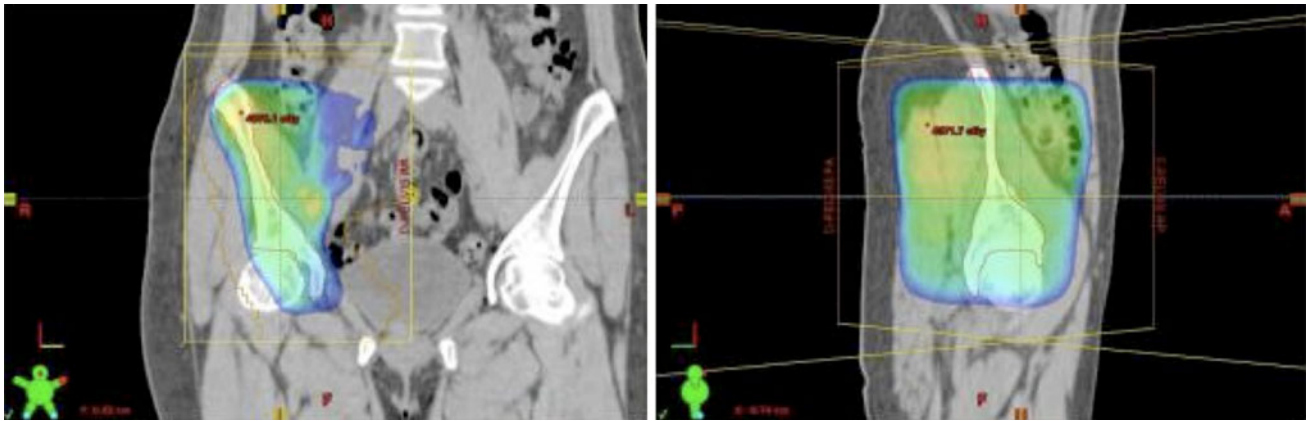


Fig. 3 Dose distribution obtained from simulation CT scan in a patient with metastatic breast cancer



Fig. 4 Photography showing abdominal wall muscle and slight overlying erythema that matched the radiation field, consistent with the diagnosis of radiation recall dermatitis

cyclophosphamide, followed by trastuzumab for 1 year and tamoxifen to complete 5 years. Two years after diagnosis, asymptomatic lung metastasis was documented. She was then offered docetaxel, carboplatin and trastuzumab-based chemotherapy and achieved a stable disease status for almost a year. After multiple progressions and different lines of chemo and hormone therapy she developed symptomatic right-sided sacroiliac joint and ischial bone metastases. She received palliative-intended radiation (39 Gy in 13 fractions with 18 MV photons) with good clinical response and no reports of skin reaction (Fig. 3). A new chemotherapy regimen based on gemcitabine 1200 mg and trastuzumab 100 mg every 3 weeks, in addition to letrozole and bisphosphonate was started. Five months after the initiation of the new chemotherapy, she referred intense abdominal pain in the right lower quadrant associated with slight erythema, warmth and tenderness of the overlying skin that matched the radiation field (Fig. 4). CT scan showed diffuse swelling of the right abdominal wall

muscles and the corresponding soft tissue. Signs of ileocolitis were also noticed (Fig. 5). Laboratory examination confirms the presence of myositis with elevation of creatine kinase to 1300 U/L. A diagnosis of RRD was made. Treatment with prednisone and NSAID was begun with partial response.

Discussion

Radiation recall dermatitis (RRD) is a rare and unpredictable phenomenon that can occur weeks, months or years after exposure to radiation. It is characterized by an acute inflammatory reaction, confined to areas previously irradiated, and usually triggered by the administration of certain drugs or sun exposure [1].

Although it is generally associated with the administration of antineoplastic chemotherapy, cases of RRD have been described with the use of other drugs such as quinolones, macrolides, statins or calcium antagonists [2–5]. D'Angio [6] published the first report in 1959, describing that dactinomycin could “reactivate” latent radiation effects in normal tissue. Since then, a series of cases have been reported, but still there are no epidemiological studies that allow us to fully characterize this syndrome. The majority of cases described occurred after exposure to monodrug treatment with anthracyclines, taxanes or anti-metabolites, especially gemcitabine and capecitabine [7–14].

Clinically, the majority of cases manifest as an acute cutaneous inflammatory reaction (dermatitis) with erythema, maculopapular or vesicular lesions, and pain followed by dry desquamation in the affected area. However, in the most severe cases might be persistent painful vesicles and necrosis. In one third of cases there is involvement of other structures besides the skin with reports describing cases of pneumonitis, myositis or enteritis [12, 15–17].

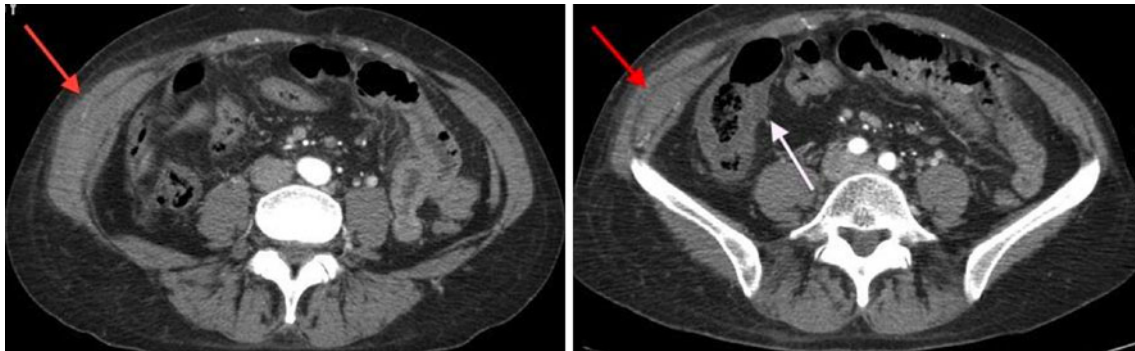


Fig. 5 CT scan of abdomen showing muscle edema and thickening (*red arrow*). Signs of colitis with submucosal edema on contrast fixation are noticed (*white arrow*)

Intense acute radiation reactions during treatment with radiotherapy are not considered a risk factor for subsequent RRD [18].

It is important to stress the difference between RRD and radiosensitization. In the latter, the effect of the radiation is enhanced during or few days after treatment with radiation therapy. In RRD the phenomenon can occur many days after the treatment has been completed, without any direct effects of radiation corresponding more to an idiosyncratic reaction [1]. The timing was set in an arbitrary way with some authors, suggesting that skin reactions brought on by drugs given less than 7 days after radiotherapy should be considered radiosensitization [1].

Even though RRD might be considered an infrequent event, being that most of the relevant information is obtained from case reports, Kodym describes its appearance in 8.8 % of 91 patients receiving palliative chemotherapy for metastatic disease [19]. It is also estimated that the probability of being diagnosed with RRD is associated with the time interval between radiation and drug exposure and RRD symptoms. A short interval between the end of radiation therapy and the beginning of chemotherapy is a known risk factor to develop the condition. Nevertheless, there are reports of cases occurring years or even decades later [20].

Based on the fact that many patients with RRD had previously received other drugs known to be also responsible, with no evidence of reaction, the response appears to be drug specific [21]. However, it is unlikely that the cytotoxic properties of chemotherapeutic agents by themselves are responsible for the phenomenon since it has an unpredictable response and in many cases the re-exposure to the drug does not produce symptom recurrence [22]. Several theories have been proposed to explain the pathophysiologic basis for RRD; however none of them has been fully validated so it remains as a poorly understood phenomenon. It has been proposed that RRD corresponds to hypersensitivity idiosyncratic drug reaction and it could be considered analogous to fixed drug eruptions [18]. Thus,

local skin reaction would be related to the continued secretion of pro-inflammatory cytokines induced by exposure to radiation and subsequently activation of a non-immune inflammatory pathway, which decreases the threshold to inflammatory response. In this scenario, the presence of a chemotherapeutic agent would trigger the overexpression of these cytokines producing the phenomenon of RRD [23].

Local vascular damage and radiation-induced depletion of stem-cells, or their inability to proliferate in situations of cytotoxic exposure, have also been hypothesized as potential etiologies of RRD [24, 25].

In the particular case of capecitabine, it has been suggested that the recall dermatitis could be caused by overexpression of the enzyme thymidylate phosphorylase, which induces angiogenesis in the irradiated area and local activation of the pro-drug in this zone [12].

In this paper, we presented two cases that illustrate the most frequent clinical presentations of RRD. The first case illustrates a dermatitis induced by the combination of capecitabine and ixabepilone with full recovery after withdrawal of the drug. Although cases of RRD have been reported with these agents used alone, this is the first case described with their combination [1, 12, 26]. In the second example we report a case of myositis associated with ileocolitis post-administration of gemcitabine and trastuzumab. Here, it is important to note that the patient presented with the classical RRD described with gemcitabine. Unlike other drugs (including trastuzumab) where dermatitis is the major manifestation, the recall reaction with gemcitabine mainly affects muscular tissue and internal organs, such as in this case [13, 27, 28]. Despite the fact that trastuzumab has been reported as a causal agent, we think it unlikely that this biological agent is responsible for RRD, based on the fact that the patient received this drug before without reporting any side effects.

The main part of the treatment involves cessation of the responsible agent. Most cases will resolve with this single action and supportive care. A rechallenge with the same

drug, using lower but more frequent doses has been successfully reported in the literature [26]. The time needed for complete healing varies with the type of offending drug, with longer times being described for oral agents [25]. Several adjuvant treatments have been described including systemic administration of corticosteroids, NSAIDs or antihistaminics according to the clinical severity of the reaction [1, 15]. Local treatment with hydrocortisone, silver sulfadiazine or sodium hyaluronate has been also used successfully [26, 29].

Conflict of interest The authors of the Manuscript: “Radiation Recall Dermatitis. Report of two cases” declare that we have no conflict of interest

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