Case Report

Radiation recall dermatitis following adjuvant capecitabine in breast cancer: A case report

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ABSTRACT

Radiation recall dermatitis (RRD) is an acute inflammation of the skin, i.e., produced by drugs, most commonly chemotherapeutic treatments, in an area of the body that has been treated with radiation in the past. This case report describes the clinical experience of a triple-negative breast cancer patient who developed RRD after postoperative radiotherapy following adjuvant capecitabine treatment. The timing of chemotherapy after radiation therapy and the improvement in radiation dermatitis following capecitabine avoidance suggest that the reaction was a true radiation recall phenomenon.

Key words: Capecitabine, Dermatitis, Radiation recall dermatitis, Triple-negative breast cancer

Radiation recall dermatitis (RRD) is an inflammatory skin reaction caused by a drug that occurs in body sites that were exposed to ionizing radiation months or years ago. In 1959, D'Angio *et al*. found that RRD was related to the use of the chemotherapeutic agent actinomycin-D [1]. Doxorubicin, docetaxel, paclitaxel, gemcitabine, and capecitabine are some of the antineoplastic drugs commonly attributed to the development of radiation recall responses. RRD can cause erythema, itching, pain, desquamation, edema, vesiculation, necrosis, ulceration, and bleeding occurring within hours to months of starting or stopping the associated drug [2-4]. Since 20–30% of RRD cases are caused by cancer medicines, recognition of RRD is extremely critical for cancer care teams to avoid erroneous diagnoses and treatments [3,4]. Studies have found that the skin is the most common site of radiation recall manifestations, with an incidence of RRD between 6% and 12% [5]. It has been theorized that the strength of radiation memory and, hence the phenomenon of radiation recall is proportional to the amount of medication taken [6]. The treatment of RRD is mostly conservative. Radiation recall reactions rarely resolve while the causative drug is being administered and require withholding the drug. Non-steroidal anti-inflammatory drugs and topical or systemic corticosteroids alleviate inflammation- although it is unclear whether corticosteroids speed up resolution. Desquamating lesions require cleaning and moist dressing with antibiotics coverage to prevent the development of infections. Antihistamines may also help. Nonetheless, the symptoms and signs may persist even if the medicine that is attributable to RRD is discontinued, particularly if irreversible skin damage has taken place [7].

Thus, it is crucial to differentiate the late, unpredictable recall phenomenon from the immediate, predictable radio sensitization phenomenon with inflammatory changes following radiotherapy (RT) treatment. A strong index of suspicion is needed for a correct diagnosis because of its rarity and the lack of specific symptoms.

CASE REPORT

A 55-year-old woman from Assam, India, was diagnosed with stage IIIB T4aN2aM0 infiltrating ductal carcinoma of the left breast in 2021. On immunohistochemistry, it was found to be a case of triple-negative breast cancer. She received neoadjuvant chemotherapy (NACT) consisting of four cycles of doxorubicin 80 mg and cyclophosphamide 800 mg, followed by four cycles of docetaxel 100 mg. Within 4 weeks of NACT, she underwent a modified radical mastectomy of the left breast on January 19, 2022. Post-operative histopathology report showed ypT2N1 stage with ductal carcinoma *in situ*,and 2 out of 17 dissected lymph nodes

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were positive for tumor cells. She was planned for adjuvant RT and received 40.05 Gy external beam RT to the left chest wall, left axilla, and left supraclavicular region in 15 fractions delivered by 6MV photons with conformal (3DCRT) technique between June 1st and 20th, 2022. She developed grade 1 dermatitis and grade 1 odynophagia, recorded as per the common terminology criteria for adverse events (CTCAE) reporting, during her RT treatment, which subsided within 6 weeks [2]. The patient was started on adjuvant capecitabine according to the results of the CREATE-X trial [8]. She began taking capecitabine 10 days following her last radiation fraction. The prescribed dose was 1250 mg/m^2 of body surface area, twice daily for 14 days with a 7-day break per cycle. After receiving the second cycle of the drug, she noticed gradually progressive erythema and dry desquamation over the skin of her left chest wall over the mastectomy site. The patient initially ignored the erythema and did not seek medical advice, but when it progressed to moist desquamation within the next 7 days, she reported it to our clinic.

On examination, the area of skin involved was from the left infraclavicular region to 5 cm below the line corresponding to the opposite inframammary fold-measuring about 15 cm × 15 cm in size (Fig. 1a). This area was corresponding to the site of RT target volumes covered with 3DCRT about 2 months ago. The grade of dermatitis was recorded as grade 3 as per the CTCAE criteria. However, no bleeding or necrosis was noted. The lesions were cleaned twice daily with normal saline. A fixed-dose combination ointment consisting of betamethasone (0.1% w/w) and neomycin (0.5% w/w) was applied topically over the lesions and then covered with moist dressing materials. An oral antibiotic for prophylaxis was also prescribed. The third cycle of capecitabine chemotherapy was withheld. Over the next 2 weeks, the dermatitis regressed to grade 1 and resolved completely over the subsequent week (Fig. 1b and c). After a week of complete resolution of dermatitis, adjuvant capecitabine was started again without dose reduction. She was examined carefully for the return of the symptoms twice weekly during chemotherapy, but they did not recur, and she safely continued her subsequent cycles.

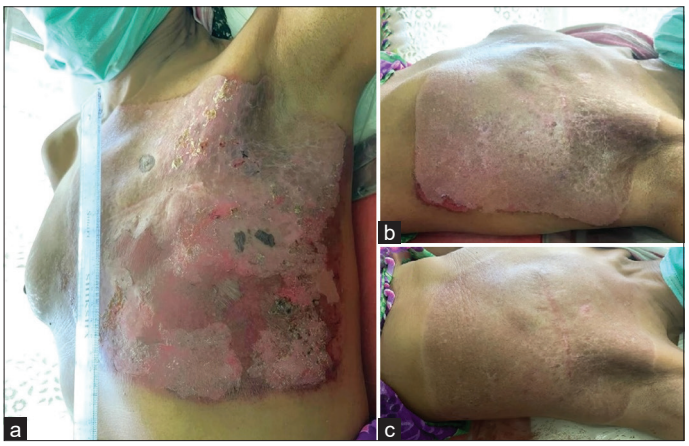

Figure 1: (a) Grade 3 Radiation recall dermatitis (RRD) with confluent moist desquamation noted over the inferior half of the skin lesion. Sharp demarcation of the lesion from the normal skin corresponding exactly over the volume of irradiated tissue indicates toward the diagnosis of RRD, (b) lesion at day 14 from initiation of conservative management showing significant improvement and (c) Complete resolution of desquamation with only mild pigmentation noted on day 21

In our case, the maximum grade of acute dermatitis noted during and at the completion of RT was grade 1, with no immediate progression reported post-RT completion. The reported flare-up of dermatitis to grade 3 occurred with an intervening period of 8 weeks after completion of RT and was induced after initiation of chemotherapy (capecitabine)-which does not fit the pathogenesis of acute radiation-induced dermatitis. From this, we concluded that it was an incident of capecitabine induced-RRD.

DISCUSSION

RRD, an acute skin inflammation, is a complex toxicity produced after RT doses in the area of irradiation caused by many systemic agents, usually chemotherapeutic drugs. Erythema, edema, vesiculation, desquamation, ulceration, and skin necrosis are the wide spectrum of manifestations that may be noticed in RRD-similar to acute radiation dermatitis (Table 1) [2]. Histopathology of the lesions often shows epidermal dysplasia, necrosis of keratinocytes, and an increase in the number of mitotic figures with infiltration by mixed inflammatory cells [9].

RRD is a rare phenomenon that may cause significant hindrances on treatment of cancer- but is often misdiagnosed and remains under-reported [3]. The deleterious effects of therapeutic radiation on the skin have been recognized, and the dose-limiting properties of skin have been understood for many years now [10]. However, the physiologic mechanism and precise etiology of RRD largely remain unknown. Multiple reasons have been proposed which include sensitivity of memory stem cells in the skin, idiosyncratic hypersensitivity, vascular factors, and lowered inflammatory threshold attributable to chemotherapy use [5-7,9].

For patients who present with skin changes localized to a site of prior radiation therapy, a high index of suspicion of RRD is to be borne in mind. A biopsy is not mandatory to confirm the diagnosis and should not be done frequently. The differential diagnoses of RRD include other common dermatological diseases such as erysipelas, herpes zoster, fungal infection, erysipelatous cancer, angiosarcoma, fixed drug reaction, and panniculitis. Literature shows that RRD has been mistaken for cellulitis because of its erythematous, heated, and painful symptoms [11]. In our example, the recent use of a recognized trigger drug, a history of radiation, with typical dermatitis over the irradiated area not responding to antibiotic treatment alone, and improvement with discontinuation of the triggering drug - clinched the diagnosis of RRD.

There is a large heterogeneity in the list of systemic therapeutic agents that may result in RRD. It has been attributed mostly to conventional chemotherapy drugs like Actinomycin-D, Adriamycin, Taxanes, and Capecitabine [5,7]. RRD in breast cancer patients has also been reported previously from the use of hormonal agents like tamoxifen and letrozole [3,4]. It has also been associated with the use of targeted therapies like Trastuzumab [12]. Furthermore, there is a lack of definite evidence on the average period of onset of RRD from the completion of RT treatment.

Table 1: Grading of radiation recall dermatitis according to common terminology criteria for adverse events, version 5 [2]

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Faint erythema, dry desquamation	Moderate to brisk erythema, patchy moist desquamation- mostly confined to skin folds and creases, moderate edema	Moist desquamation in areas other than skin folds and crease, bleeding induced on abrasions or minor trauma	Life-threatening consequences- skin necrosis, ulceration involving full thickness of dermis, spontaneous bleed from site: skin graft is indicated	Death

An observational study suggested that a short interval between 6 and 37 days from the end of RT to the initiation of chemotherapy predisposes the development of RRD [13]. However, incidences of RRD have been reported as late as 15 years from the end of RT with the use of Adriamycin chemotherapy [14]. Furthermore, no clear RT dose threshold or site predilection could be established yet for the development of RRD [9].

Management of RRD depends on the severity of symptoms and is mostly conservative- with moisturizers, antihistamines, or emollients. Glucocorticoids, whether topical or systemic, may help reduce the inflammation but are typically not curative. Severe cases, as in our patient with grade 3 signs and symptoms, require interruption of the causative medication till full symptom resolution [12]. Dose reduction during reintroduction of the triggering chemotherapeutic agent is thought to decrease the chances of recurrent RRD [6]. In our case, there was early initiation of chemotherapy - on 10th day post-RT, which could have contributed to the development of RRD as suggested by Kodym *et al*. [13]. The structural modifications brought about by mastectomy may have further contributed to the susceptibility of epithelial tissue to RRD in our case. Fortunately, the symptoms of RRD did not recur after rechallenge by the same drug (capecitabine) without dose reduction, and the patient successfully completed her adjuvant chemotherapy.

Capecitabine is now being increasingly used in breast cancer patients post-RT as it has been shown to improve survival in her-2 negative cases with residual disease following NACT [9]. The mechanism of RRD after capecitabine use has been explained by Lee *et al.* and Saif *et al.* [7,15]. Thymidine phosphorylase, a potent angiogenic factor, has been associated with the development of radiation recall due to capecitabine. Any oxidative stress upon cancer cells results in overexpression of the enzyme thymidine phosphorylase, thereby resulting in stress-induced angiogenesis. In our case, it can be hypothesized that prior RT which upregulated thymidine phosphorylase in the cells of the irradiated site, caused angiogenesis to develop in that area. The resultant hypervascularity and erythema were aggravated by the early introduction of capecitabine- contributing to a synergistic effect-ultimately manifesting as RRD.

CONCLUSION

We report a rare instance of RRD due to adjuvant capecitabine chemotherapy in a middle-aged female breast cancer patient. Radiation and medical oncologists must be vigilant of this rare but treatment-limiting toxicity while prescribing capecitabine in breast cancer patients following RT.

REFERENCES

1. D'angio GJ, Farber S, Maddock CL. Potentiation of x-ray effects by actinomycin D. Radiology 1959;73:175-7.
2. Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. Using the common terminology criteria for adverse events (CTCAE-version 5.0) to evaluate the severity of adverse events of anticancer therapies. Actas Dermosifiliogr (Engl Ed) 2021;112:90-2.
3. Barco I, Fraile M, Vidal M, Cambra MJ, Vallejo E, Deu J, *et al*. Tamoxifen induced radiation recall dermatitis in a breast cancer patient. Breast J 2018;24:662-3.
4. Sweren E, Aravind P, Dembinski R, Klein C, Habibi M, Kerns ML. Radiation recall dermatitis following letrozole administration in patient with a remote history of radiation therapy. NPJ Breast Cancer 2021;7:62.
5. Burris HA 3rd, Hurtig J. Radiation recall with anticancer agents. Oncologist 2010;15:1227-37.
6. Camidge R, Price A. Characterizing the phenomenon of radiation recall dermatitis. Radiother Oncol 2001;59:237-45.
7. Lee V, Lam KO, Kwong D, Leung TW. Radiation recall after capecitabine in a patient with recurrent nasopharyngeal carcinoma: A case report. J Med Case Rep 2016;10:247.
8. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, *et al*. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 2017;376:2147-59.
9. Laird J, Leventhal J, Kanowitz J, Damast S. Radiation recall dermatitis after capecitabine in a patient with triple negative breast cancer. Pract Radiat Oncol 2021;11:448-52.
10. Kole AJ, Kole L, Moran MS. Acute radiation dermatitis in breast cancer patients: Challenges and solutions. Breast Cancer (Dove Med Press) 2017;9:313-23.
11. Ristić B. Radiation recall dermatitis. Int J Dermatol 2004;43:627-31.
12. Moon D, Koo JS, Suh CO, Yoon CY, Bae J, Lee S. Radiation recall dermatitis induced by trastuzumab. Breast Cancer 2016;23:159-63.
13. Kodym E, Kalinska R, Ehringfeld C, Sterbik-Lamina A, Kodym R, Hohenberg G. Frequency of radiation recall dermatitis in adult cancer patients. Onkologie 2005;28:18-21.
14. Burdon J, Bell R, Sullivan J, Henderson M. Adriamycin-induced recall phenomenon 15 years after radiotherapy. JAMA 1978;239:931.
15. Saif MW, Black G, Johnson M, Russo S, Diasio R. Radiation recall phenomenon secondary to capecitabine: Possible role of thymidine phosphorylase. Cancer Chemother Pharmacol 2006;58:771-5.

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