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Original Research

Radiation Recall Dermatitis in Carcinoma Breast: A Decade of Experience from a Tertiary Cancer Center in North West India

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Aim: This study investigates the occurrence of radiation recall dermatitis (RRD), an acute inflammatory reaction triggered by chemotherapy in previously irradiated areas. RRD manifests in nearly two thirds of cases as skin reactions, ranging from mild erythema to severe desquamation. Our objective was to evaluate the frequency, severity and clinical pattern of RRD in breast cancer patients treated with radiotherapy.

Materials and Methods: Data were retrospectively reviewed for 3462 breast cancer patients who underwent radiation therapy. Follow-ups were conducted weekly during chemotherapy, monthly for the initial 3 months, every 3 monthly up to 1 year, and biannually thereafter. The severity of dermatitis was graded using Radiation Therapy Oncology Group (RTOG) criteria, and supportive skin care was provided as needed. Patients included in the study had pathologically confirmed breast cancer, underwent modified radicle mastectomy, and received chest wall radiotherapy (40.05 Gy in 15 fractions; 2.67 Gy per fraction, 5 fraction per week for 3 weeks).

Results: RDD was reported in 359 patients of 3462 (10.36%) following the administration of chemotherapy. The majority of cases (302 patients, 84.12%) occurred between 3rd week and the 2nd month post-chemotherapy. Grade 1 reactions were observed in 258 patients (71.86%), grade 2 in 85 patients (23.67%) and grade 3 in 16 patients (4.45%). Most RRD cases were associated with Adriamycin/doxorubicin, although other agents also agents also contributed. All patients responded favourably to topical steroids, with complete resolution and satisfactory skin appearance by 6 months. The latest reported case of RRD occurred 5 years post-radiotherapy and linked to administration of Paclitaxel and Carboplatin.

Conclusion: This study highlights the frequency, timing and severity of RRD in breast cancer patients treated with radiotherapy and subsequent chemotherapy. While anthracyclines such as Doxorubicin are the most common culprits, other agents, including alkylating agents, antimetabolites and even exposure to UV light are also implicated. The unpredictable interval between radiotherapy and RRD onset, ranging from days to years, underscores the need for ongoing research to better understand this phenomenon.

Introduction

Radiation recall, also referred to as radiation recall dermatitis (RRD), is an acute inflammatory reaction that occurs in previously irradiated skin when exposed to certain response inducing drugs. This phenomenon, first identified by D'Angio in 1959, was initially linked to the drug dactinomycin [1]. Despite its recognition, the precise cause of RRD remains unclear, and its onset is unpredictable [2]. The condition is most often triggered by antineoplastic drugs, including doxorubicin, gemcitabine, paclitaxel, docetaxel, dactinomycin, vinblastine, carboplatin, methotrexate, capecitabine, transtuzumab etc [3]. Non-cancer drugs, such as UV radiation, phentermine and certain antibiotics (levofloxacin) and anti-estrogenic drugs such as tamoxifen have also been implicated [4, 5]. However, predicting which drug will trigger RRD in individual patients is currently impossible, and re-exposure to the same drug may not always result in a reaction [6]. RRD manifests in various ways, from mild skin redness to severe ulceration, influenced by factors such as radiation dose, the timing of drug administration, and patient characteristics [7]. The mechanisms underlying this reaction remain under investigation, with hypotheses ranging from hypersensitivity to previously irradiated tissue to immune system activation [8]. Preventing RRD is difficult, but strategies like increasing the interval between radiotherapy and chemotherapy can reduce the likelihood of occurrence [9]. While reactions usually develop days to weeks after drug exposure, delayed cases, even months after radiation, have also been reported [3]. Early identification and treatment of RRD are essential to reducing patient discomfort and complications.

Materials and Methods

Study Setting

This retrospective study was conducted at a regional tertiary cancer centre in northwest India. Between January 1, 2013, and December 31, 2023, 8930 new breast cancer patients were registered, with 3462 confirmed cases of ductal carcinoma included in the study. Exclusion criteria are detailed in Table 1 and Figure 1.

Total newly diagnosed cases (2013-2023)	8930
Exclusion Creteria	No of Cases
Histology Other than Ductal Carcinoma	329
Radiotherapy received at other institute/ refused for radiotherapy	731
Patient lost to follow up / expired	521
Male Breast Carcinoma	137
Patient who didn't receive Radiotherapy	
Stage-4	2132
Stage-1	462
Stage -2 with node negative	342
Other patient not fit into inclusion criteria	823
Cases Included in Study (After Exclusion)	3462

Table 1. Enrolment of Patients into the Study.

Figure 1.Exclusion criteria.

Treatment Protocols: The average age of participants was 51 years (range: 30–75 years). Patients were staged according to the TNM system [10]. Initial treatments involved surgery (modified radical mastectomy) followed by radiotherapy and chemotherapy. For locally advanced cases, 2–3 cycles of neoadjuvant chemotherapy were given before surgery to reduce the volume of tumor. After surgery, patients underwent chest wall irradiation (40.05 Gy in 15 fractions, at 2.66 Gy per fraction over three weeks). Chemotherapy, typically consisting of 3–6 cycles, was administered after radiation therapy.

Follow-Up: Patients were monitored weekly during chemotherapy, monthly for the initial three months, and then every three monthly for one year, transitioning to six-month intervals. RRD was observed from chemotherapy initiation until December 2023, with a median follow-up of 3.6 years. Radiation dermatitis and recall reactions were classified using RTOG/ EORTC criteria [11] (Table 2).

S.No.	Chemotherapy regimes	No. of patientsreceiving CT after RT	Total no. of patient developing RRD	% of patientsdeveloping RRD
1	CAF Regime	362	46	12.77
2	Adriamycin + Cyclophosphamide	1438	186	12.93
3	Epirubicin + Cyclophosphamide	412	17	4.12
4	Cyclo + Mtx + 5 FU	219	16	7.30
5	Docetaxel + Adriamycin	90	11	12.22
6	Paclitaxel + Adriamycin	126	14	11.11
7	Gemcitabine + Carboplatin	132	8	6.06
8	Paclitaxel + Carboplatin	428	22	5.14
9	Docetaxel	96	2	2.08
10	Paclitaxel	159	3	1.88

Table 2. Frequency of Radiation Recall Dermatitis According to the Chemotherapeutic Agents/regimes.

Results

Incidence and Timing: Radiation recall dermatitis occurred in 359 of 3462 patients (10.36%) who received chemotherapy after radiotherapy. The majority of cases (302, 84.12%) occurred between the third week and the second month after chemotherapy. Severity and Dose:

• Grade I: Mild reactions were observed in 71.86% (258) patients.

• Grade II: Moderate reactions were seen in 23.67% (85) patients.

• Grade III: Severe reactions were reported in 4.45% (16 patients).

The median radiation dose at which dermatitis developed was 36.4 Gy (range: 30–50 Gy).

Management and Outcomes: All patients responded well to topical steroids, with full skin recovery within six months. The majority of reactions (70.5%) were linked to anthracycline-based chemotherapy regimens, particularly doxorubicin. The latest case of RRD in this cohort occurred one year after radiotherapy following the administration of doxorubicin.

At 6 months the appearance of the skin remained good in all cases. All these patients had received

chemotherapy after completion of radiation. All cases had good response to topical steroids. Last case in our study developed RRD at 5 years after radiation, with administration of Paclitaxel and Carboplatin.

Discussion

Radiation recall dermatitis is a distinct phenomenon from acute radiation-induced dermatitis. Unlike immediate reactions during radiotherapy, RRD occurs after initial resolution of radiation-induced dermatitis and can be triggered by subsequent drug exposure [12]. The incidence of RRD has been reported between 1% and 10% in various studies, with our study showing a 8.4% incidence [13].

In our study, 19.75% of patients who started chemotherapy within four weeks of radiotherapy experienced RRD, compared to only 5.10% of those who started later.

Pathophysiology

Although the mechanisms behind RRD remain debated, several potential causes include:

1. Sub-lethal Damage: Cells exposed to radiation may become hypersensitive to later cytotoxic drugs [14].

After completion of radiation therapy, the tissue seems healed but with defect in the surviving cells, which shows enhanced response to chemotherapeutic agents, in form of RRD.

1. Immune Response: RRD could be a result of immune-mediated activation, arising as a result of the damage incurred by previous radiotherapy event, similar to the Koebner phenomenon [15].

2. Stem Cell Depletion: The loss of tissue stem cells may render surviving cells more susceptible to further damage [16]. RRD can affect not only the skin but also mucosal tissues, the lungs, the gastrointestinal tract, and even the central nervous system [10].

Short intervals between radiotherapy and chemotherapy are a significant risk factor for developing RRD [17]. Camidge and Price advocated that the reaction should be considered to be RRD only if the time lag is 7 days. They reported the median gap to be 40 days for RRD in relation to various systemic drugs. In our study, the median time gap was 30 days. However, there are few reports of RRD occurring years after radiation.

Burdon et al. [13] reported a case of radiation recall ulceration stomatitis triggered by doxorubicin 15 years after radiotherapy. In our study, the last case of RRD was seen after 5 year. In another patient, RRD triggered by pemetrexed administration 25 years after radiotherapy, and the reaction recurred upon re-challenge.

Similarly, in a study by Saif et al. [16], one out of the 20 patients who received previous combination therapy with capecitabine and radiotherapy, developed radiation recall when re-treated with capecitabine after 4 weeks.

Yeo at al. [10] reported that among 32 patients treated with docetaxel (8 as mono-therapy and 24 as combination therapy), 2 patients (6%) developed radiation recall. In a retrospective review of 171 previously irradiated patients who subsequently received docetaxel, 3 patients (1.8%) developed RRD. In our study, 71.58 % of RRD cases were seen in patients who received Adriamycin based chemotherapy regimens followed by 14.48% cases in taxane based chemotherapy regimens.

However, it is difficult to predict which drug among the regimen is the culprit.

The timing of initiation of chemotherapy after completion of radiotherapy may play a crucial role in the development of RRD. In the American Society of Breast Surgeons Mammosite Breast Brachytherapy Registry trial, 9 out of 50 (18%) breast cancer patients receiving chemotherapy 3 weeks after radiotherapy developed RRD, as compared to 6 out of 81 (7.4%) patients receiving chemotherapy >3 weeks after radiotherapy (p=0.09). The incidence of RRD dramatically increased to 28.6% in patients who received chemotherapy within 1 week of radiotherapy in this study; however, reactions arising in this time frame are difficult to be differentiated from radio-sensitization.

In our study 196 out of 992 (19.75%) breast cancer patients receiving chemotherapy ≤ 4 weeks after radiotherapy developed RRD, as compared to 1426 out of 2470 (5.10%) patients receiving chemotherapy >4 weeks after radiotherapy (p=0.09). It has also been reported that the severity of RRD tends to be greater when there is a shorter time gap between radiation and the precipitating agent, but there is no definitive association. It can be concurred that RRD occurs as a result of a complex interplay between the radiation regimen, the chemotherapeutic agent and the timing." [6, 13, 15, 16]. No relationship has been established between the occurrence of RRD and the radiation dose. The RRD has been reported in treatment schedules well below 20 Gy. 13 In our study, all the patients received a total dose of 40.05 Gy. In the cases of breast conserving therapy the incidence of RRD predominantly depends on the breast volume, the beam energy and the use of IMRT [19].

Caloglu et al have proposed an algorithm on how to manage the recall phenomena. In cases of severe reactions, they suggest prescribing systemic or topical steroids, non- steroidal anti-inflammatory agents, and antihistamines. The available scoring system subdivides RRD into the usual grades I to V.22 The time over which RRD resolves depend upon the pharmacokinetics of the precipitating agent, and reactions are more likely to resolve rapidly after discontinuation of intravenous administration than oral. Reactions tend to resolve within days or 1-2 weeks. Protection of the skin is important and patients should be advised to stay out of the sun or use sunscreens, avoid tanning beds, and wear loose, non-restrictive cotton clothing.

Management Strategies

The treatment for RRD varies based on severity and includes corticosteroids, NSAIDs, and antihistamines [18]. Preventative strategies such as delaying chemotherapy after radiotherapy have proven effective in reducing the incidence of RRD [19].

In conclusion, this study underscores the importance of early recognition and management of RRD, particularly among breast cancer patients receiving anthracycline and taxane-based regimens post-radiotherapy. Radiation may induce cells to secrete low levels of cytokines like TNF, which are up regulated, causing a recall reaction. Often, the recall reaction is more severe than the original radiation induced reaction. Although it is not possible to predict which drug may cause RRD, but as observed in our study, the majority of cases were seen in patients who received anthracycline or taxane based chemotherapy. So, the treating physicians need to have a high index of suspicion while administration of these chemotherapy regimens in previously irradiated patients. Extending the interval between radiotherapy and chemotherapy can significantly reduce the likelihood of RRD. Proactive monitoring and timely intervention are critical for improving patient outcomes and reducing the discomfort associated with this reaction.

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Conflict of Interest

Author declares no conflict of interest.

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