Radiation Recall Dermatitis in Breast Cancer Patient after Trastuzumab: A Case Report with Review of Literature

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Abstract

Radiation recall dermatitis (RRD) is an extremely rare phenomenon. A variety of factors such as antineoplastic agents, pharmaceutical agents, physical and environmental factors have been proposed to be the underlying cause of RRD. Only a handful cases have been reported till date, where trastuzumab is sought to be the triggering agent. The presentation of RRD varies from mild erythematous to extensive confluent dermatitis, resolving over a period of 1 to 2 weeks with conservative management. Most of the patients tend to tolerate rechallenge well without showing reappearance. We hereby describe a lady with breast cancer having RRD following administration of trastuzumab. She developed reaction 28 days post-radiotherapy and managed conservatively. Furthermore, she was rechallenged with the same dose, that she tolerated very well, without any reappearance. Hence, an acquaintance of the clinicians to this rare entity is essential for timely diagnosis and appropriate management.

Keywords
- radiation recall dermatitis
- trastuzumab
- radiation recall phenomenon

Introduction

Radiation recall is an ill-defined inflammatory phenomenon characterized by reactions triggered by exposure to a certain agent in the previously irradiated region.[1] It is triggered by post-radiation exposure to certain offending agents including antineoplastic and other pharmacological agents, physical and environmental factors.[1–3] Radiation recall dermatitis (RRD) is the most common manifestation of radiation recall phenomenon.[3] The first documented evidence of RRD was reported long back in 1959 by D'Angio et al.[4] Presently more than hundred cases have been reported in the form of either isolated case reports or small case series. The estimated incidence of RRD is around 6 to 8%.[1–3]

We report a case of RRD in breast cancer patient triggered by trastuzumab along with a review of literature of similar cases. A literature review was done for all published case reports or case series in English language on RRD with trastuzumab using the keywords "radiation recall dermatitis," "trastuzumab," and "radiation recall phenomenon."

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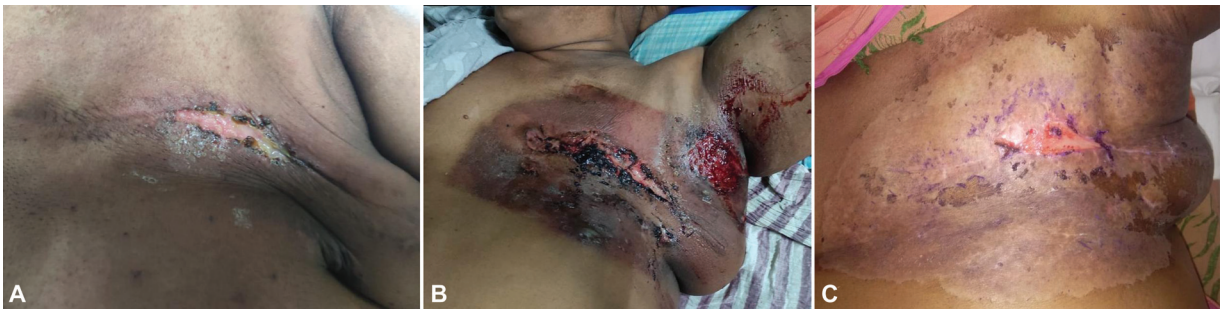

Fig. 1 (**A**) Area of moist desquamation, 7 days post-LRRT. (**B**) Radiation recall dermatitis (RRD), 14 days post-trastuzumab, 28 days post-LRRT. Reaction was well demarcating radiation chest wall portals. (**C**) Near complete resolution of RRD with small persistent area of moist desquamation along the scar, 42 days post-LRRT. LRRT, locoregional radiotherapy.

Case Report

A 59-year-old postmenopausal hypertensive lady without any significant family history or any history of allergy evaluated for a 5×4 cm lump in the left breast and a 1×1 mobile axillary lymph node in June 2021. Histopathology confirmed it as invasive breast carcinoma, no special type, grade 3, hormone receptor positive (estrogen receptor: Allred score—8, progesterone receptor: Allred score— 7) and Her 2 Neu positive on immuno-histochemistry. Staging 18F-fluorodeoxyglucose positron emission tomography/computed tomography scan depicted a soft tissue lesion of 49×42 mm in upper inner quadrant with a small satellite nodule in lower outer quadrant along with axillary lymph nodes without any distant metastases. She received three cycles of multiagent neoadjuvant chemotherapy consisting TCH regimen (docetaxel 75 mg/m^2, carboplatin area under the curve 6, and trastuzumab loading dose of 6 mg/kg followed by 4 mg/kg) that led to partial clinicoradiological partial response. She underwent modified radical mastectomy 4 weeks after completion of chemotherapy. The final histopathology report revealed a unifocal tumor of maximum size of 2 cm with 1 out of 38 dissected lymph nodes was positive without extranodal extension (stage- ypT1c ypN1a). Later, she received adjuvant chemotherapy with three more cycles of TCH. Further, she was started on three weekly maintenance trastuzumab along with anastrozole.

Four weeks post-adjuvant TCH and one week after seventh cycle of trastuzumab, she received locoregional radiotherapy (LRRT) targeting left chest wall (CW) and left supraclavicle fossa (SCF). LRRT was delivered using 6 MV photons to a total dose of 40 Gy in 15 fractions over a period of 3 weeks via bitangential portals for CW and a single anterior portal for SCF radiation. The entire treatment was performed by deep inspiratory breath hold technique and a 5 mm thick bolus was placed throughout the course of radiation over the CW for adequate coverage of the skin. Maximum dose (D max) to the planning target volume (PTV) was 107.2% and volume receiving 105% (V105%) was 11.6 cc; all the other dosimetric parameters for PTV and organs at risk were within the predefined limits.[5] She tolerated LRRT well and at the end of LRRT, she had radiation therapy oncology group (RTOG) grade 1 dermatitis and grade 1 esophagitis at the completion of radiation that were well managed with topical steroid creams and anesthetic antacid gel. In the last week of LRRT, she received her eighth cycle of trastuzumab without any undue toxicity. After 1 week of completion of LRRT, she presented with focal moist desquamation along the scar over the CW (►**Fig. 1A**) for which she was prescribed placental extract gel. Two weeks later, ninth cycle of trastuzumab was given (14 days post-LRRT).

In the subsequent week, she had progressive worsening of dermatitis and after 2 weeks (28 days post-LRRT), she landed up with worsening RTOG grade 3 dermatitis. Intense dermatitis in the form of ulceration, small areas of hemorrhage, was noted over the entire CW (►**Fig. 1B**). However, the reaction was restricted within the LRRT portals and no reaction was observed outside the irradiated region, leading to the diagnosis of RRD. She was managed with topical 1% gentian violet (GV) application along with analgesics. There were no signs or evidence or any superadded infection. Surprisingly, no reaction was observed over the site of SCF irradiation. High-resolution computed tomography chest ruled out underlying recall pneumonitis. Gradually over a period of 3 weeks (42 days post-LRRT), the reaction showed significant improvement with near complete resolution with a persistent small area of moist desquamation along the scar that healed completely in next 2 weeks (►**Fig. 1C**). After 40 days from ninth cycle (54 days post-LRRT), she was rechallenged with the same dose of trastuzumab, without any reappearance of recall reaction.

Discussion

RRD is a well-known entity but largely under-reported.[1] Most of the reported cases are with chemotherapy agents,[2,6,7] followed by some non-neoplastic agents,[8,9] physical agents,[3,10] and other pharmaceutics.[11,12] However, only a few case reports highlight this reaction following targeted therapies[13] including trastuzumab.[13–19] The overexpression of the HER2 is observed in 20 to 30% of primary breast cancers[20] and trastuzumab is a recombinant humanized immunoglobulin G1 monoclonal antibody against HER2, indicated for the management of both primary breast cancer and metastatic disease.[20] The most serious and/or common adverse reactions reported with trastuzumab usage are cardiac dysfunction, infusion-related reactions, neutropenia, and pulmonary adverse reactions.[20] Although dermatitis

with severity ranging from mild-to-moderate has been reported with the use trastuzumab,[20,21] radiation recall is extremely rare and all documented cases have developed reaction to the irradiated skin (RRD),[13–19] with only a single reported case of radiation recall pneumonitis[17] till date.

All cases depicting RRD triggered by trastuzumab[13–19] are summarized in ►**Table 1**. Average duration between radiotherapy (RT) and occurrence of RRD was noted to be 135 days (range: 29–283 days). The triggering cycle of trastuzumab for development of RRD and the cumulative doses at the occurrence of RRD are highly variable in the literature. Moreover, the development of RRD does not seem to be related to RT tolerance as most of the patients developed RRD despite a good tolerance. The RT dose fractionation and target volumes also do not seem to have any corelation with the incidence or intensity of RRD, as majority of these cases are reported with hypofractionated LRRT. However, Alsabbak et al have observed the reaction all over the treated region of breast but with an increased intensity over the area of RT boost region.[14]

Anupama et al have reported an identical incidence of RRD to the present case.[19] In her case, the reaction was occurred 28 days post-LRRT and it was limited to CW region only. We have noticed the reaction only in the irradiated CW and SCF did not show any recall reaction. Such incidences of discriminated RRD have also been reported previously[22] However, exact pathophysiology of these type of reactions is not yet been described in the literature.[1] Various postulated hypotheses include depletion or changes in performance of irradiated stem cells,[1,23] idiosyncratic reaction to triggering agents,[2] vascular endothelial damage,[2] altered immunological responses, and upregulation of specific enzymes that activate prodrug locally in previously irradiated region.[2,24] It has also been postulated that cumulative DNA damage along with oxidative stress may play a role in RRD.[2] Also, histopathological confirmation is not required unless clinical scenario leads to a high suspicion of recurrence.[23] Histological features show changes identical to radiation dermatitis consisting epidermal dysplasia, necrosis of keratinocytes, ballooning degeneration, increased mitotic figures, and inflammatory infiltrates.[23]

Most reported incidences of RRD are of mild-to-moderate grade and rarely lead to life-threatening reactions.[2,6] Also, in our review of literature, all cases of RRD triggered by trastuzumab were of mild-to-moderate intensity and well managed with oral antihistamines, local steroid, or antibiotic cream. No standard set of guidelines exist for the management of these reactions.[2,6] However, discontinuation of triggering agent or delaying further exposure proposed to be the most important measure.[2,6,25] Decision for the symptomatic management with topical moisturizers, steroidal creams, and other anti-inflammatory agents should be individualized on the bases of severity of reaction.[2,6,25] In the present case, alongside analgesics, we have used topical 1% GV. Antifungal and antiseptic properties of topical GV have been used to manage radiation dermatitis and burnt cases traditionally.[26] Most of these cases have shown a near complete resolution within 2 to 7 days, but an intermittent pain may persist for a longer duration. Rechallenging the same triggering agent in most of the instances does not lead

Table 1 Reported incidences of RRD triggered by trastuzumab

Sr. No.	Author	Patient characteristics	Radiotherapy details	Triggering agent	Description of RRD	Treatment and outcome	Rechallenge
1.	Shrimali et al, 2009[16]	A 71-year-old female with breast cancer, history of allergies: NR	45Gy in 20# to CW and SCF, at conclusion she had erythematous dermatitis	Trastuzumab (dose: NS) every 3 weeks with anastrozole (1mg/day), started 42 days after RT	Mild, asymptomatic erythematous RRD noticed 3 weeks after first cycle (62 days after RT)	Intravenous hydrocortisone and oral paracetamol. Complete resolution of RRD (duration: NS)	Yes, under steroid coverage with same dose, without reappearance
2.	Chung et al, 2009[18]	A 41-year-old female with breast cancer, history of eczema, allergic rhinitis, and contact dermatitis to numerous allergens	42.5Gy in 16# to WB and 10 Gy TBB and 37.5Gy in 16# to SCF, IMN, and axilla. Post-RT she had brisk erythema and moist desquamation over inframammary fold	Trastuzumab (513.28 mg) IV every 3 weeks, started 28 days after RT	Mild, painful, swollen, erythematous RRD, 3 days after 12th cycle (283 days post-RT)	Nil. Brisk erythema resolved spontaneously within 2 days, pain persisted for ~14 days	Yes, without reappearance
3.	Moon et al, 2013[15]	A 55-year-old female with breast cancer, no past history of allergies	45Gy in 25# to WB, SCF and IMN, axilla with TBB 9Gy in 5#. At conclusion she had erythematous dermatitis	Trastuzumab (6mg/kg) every 3 weeks, 45 days after RT	Mild, erythematous RRD, noticed 9 days after fifth cycle (159 days post-RT)	Nil. Resolved completely in 7 days	Yes, same dose, without reappearance
4.	Alsabbak et al, 2013[14]	A 47-year-old female with breast cancer, history of allergies: NR	50 Gy in25# to CW and 14Gy in 7# boost to area of positive margins by 9 MeV electrons with 1 cm bolus. At conclusion she had erythematous dermatitis with a small area of desquamation	Trastuzumab (dose: NS) every 3 weeks, continued during RT	Mild, erythematous RRD 2 weeks after third cycle (56 days post-RT). RRD was most prominent in the area of boost	Benadryl and topical steroid. Complete resolution of RRD (duration: NS)	Yes, after 3 weeks. No reappearance

(*Continued*)

Table 1 (*Continued*)

Sr. No.	Author	Patient characteristics	Radiotherapy details	Triggering agent	Description of RRD	Treatment and outcome	Rechallenge
5.	Levy et al, 2013[13]	Age: NS, female with breast cancer, history of allergy: NR	50Gy in 25#, Site: NS	Trastuzumab (dose: NS), started 25 weeks after RT	Severity of RRD: NS, developed in 2 weeks after exposure (189 days post-RT)	NS	NS
6.	Lee et al, 2014[17]	A 55-year-old female with fibroadenoma of breast with axillary metastases, history of allergy: NR	50.4Gy in 20# to WB	Trastuzumab (dose: NS) every 3 weeks, started 10 days after RT	Mild, erythematous RRD and edematous plaques, developed 24 weeks after RT (168 days post-RT) along with radiation recall pneumonitis	Prednisolone, 30mg, Improvement in 2 weeks	NS
7.	Anupama et al 2018[19]	A 56-year-old female with breast cancer, past history of allergies: No	40 Gy/15# to CW and SCF, at conclusion: mild erythematous dermatitis	Trastuzumab (450mg) every 4 weeks, started 4 weeks after RT	Mild-to-moderate, painful, swollen and erythematous, maculopapular RRD with discoloration, next day of first cycle (29 days post-RT)	Topical betamethasone cream, erythema reduced in 2 days but pain persisted for 2 weeks	Yes, after 4 weeks, no reappearance

Abbreviations: CW: chest wall, IMN: internal mammary nodes, IV: intravenous, NR: not reported, NS: not specified, RRD: radiation recall dermatitis, RT: radiotherapy, SCF: supra-clavicular fossa, TBB: tumor bed boost, WB: whole breast, #: number of fractions

to reappearance of RRD.[1,2,6] However, for oncological benefit, continuation of offending agents with added protective measures and under careful surveillance even during reaction has also been reported and it may not worsen the reaction further.[1,2,6]

Hence, though the incidence of radiation recall is rare, its diagnosis is likely to be made more frequently in modern oncology practice and oncologists should be aware of this phenomenon. A robust systematic review with inclusion of all reported cases and case series to characterize this unpredictable clinical phenomenon will add immense knowledge for the management and prognosis of radiation recall and hence, it is highly recommended.

Conclusion

In the current multidisciplinary era of cancer management, oncologists should be aware of radiation recall phenomenon with trastuzumab so as to aid for a timely diagnosis and intervention. Moreover, until the exact pathophysiological mechanism and predictors radiation recall is understood, oncologists should report such cases encountered in their day-to-day practice.

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Conflict of Interest
None declared.

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