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.”
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/m², carboplatin area under the curve 6, and trastuzumab loading dose of 6 mg/kg followed by 4 mg/kg) that led to partial clinicoradiological 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 therapies13 including trastuzumab.13–19 The overexpression of the HER2 is observed in 20 to 30% of primary breast cancers20 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
traditionally. Most of these cases have shown a near complete resolution within 2 to 7 days. Rechallenging the same triggering agent in most of the instances does not lead to the reaction all over the treated region of breast but with an increased intensity of RRD and the cumulative doses at the occurrence of RRD and the cumulative doses at the occurrence of RRD do not show any recall reaction. Such incidences of discriminated reaction to the irradiated skin (RRD), as majority of these cases are reported with idiopathic Dermatitis with Trastuzumab.

Table 1 Reported incidences of RRD triggered by trastuzumab

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Author Patient characteristics</th>
<th>Radiotherapy details</th>
<th>Triggering agent</th>
<th>Description of RRD</th>
<th>Treatment and outcome</th>
<th>Rechallenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Shrimali et al, 2009**</td>
<td>A 71-year-old female with breast cancer, history of allergies: NR</td>
<td>45 Gy in 2# to CW and SCF, at conclusion she had erythematous dermatitis</td>
<td>Trastuzumab (dose: NS every 3 weeks with anastrazole (1 mg/day), started 42 days after RT)</td>
<td>Mild, asymptomatic erythematous RRD noticed 3 weeks after first cycle (62 days after RT)</td>
<td>Intravenous hydrocortisone and oral paracetamol. Complete resolution of RRD (duration: NS)</td>
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<tr>
<td>2.</td>
<td>Chung et al, 2009**</td>
<td>A 41-year-old female with breast cancer, history of eczema, allergic rhinitis, and contact dermatitis to numerous allergens</td>
<td>42.5 Gy in 16# to WB and 10 Gy TBB and 37.5 Gy in 16# to SCF, IMN, and axilla. Post-RT she had brisk erythema and moist desquamation over inframammary fold</td>
<td>Trastuzumab (513.28 mg) IV every 3 weeks, started 28 days after RT</td>
<td>Mild, symptomatic RRD, 3 days after 12th cycle (283 days post-RT)</td>
<td>Nil. Resolved spontaneously within 2 days, pain persisted for ~14 days</td>
</tr>
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<td>3.</td>
<td>Moon et al, 2013**</td>
<td>A 55-year-old female with breast cancer, no past history of allergies</td>
<td>45 Gy in 2# to WB, SCF and IMN, axilla with TBB 9 Gy in 5#. At conclusion she had erythematous dermatitis</td>
<td>Trastuzumab (6 mg/kg) every 3 weeks, 45 days after RT</td>
<td>Mild, erythematous RRD, noticed 9 days after fifth cycle (159 days post-RT)</td>
<td>Nil. Resolved completely in 7 days</td>
</tr>
<tr>
<td>4.</td>
<td>AlSabbak et al, 2013**</td>
<td>A 47-year-old female with breast cancer, history of allergies: NR</td>
<td>50 Gy in 2# to CW and 14 Gy 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</td>
<td>Trastuzumab (dose: NS every 3 weeks, continued during RT)</td>
<td>Mild, erythematous RRD 2 weeks after third cycle (56 days post-RT). RRD was most prominent in the area of boost</td>
<td>Benadryl and topical steroid. Complete resolution of RRD (duration: NS)</td>
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</tbody>
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(Continued)
to reappearance of RRD. However, for oncological benefit, continuation of offending agents with added protective measures and under careful surveillance even during reac-tion has also been reported and it may not worsen the reaction further.

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, 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.

Table 1 (Continued)

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

References
chemoradiotherapy organ preservation protocol. Eur Arch Otorhinolaryngol 2007;264(09):1099–1102