

# Radiation recall dermatitis induced by a second course of radiation therapy in the absence of clinically significant field overlap

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## Abstract

Radiation recall is a phenomenon wherein an acute inflammatory reaction occurs in a previously irradiated field upon exposure to a subsequent agent months or even years after radiation therapy. Common causative agents include systemic therapy, such as chemotherapeutics or antibiotics. In the literature, these agents have been reported to trigger a variety of radiation recall reactions, most frequently dermatitis. We present the first documented case of radiation therapy-induced radiation recall dermatitis and postulate a hypothesis for its mechanism of action.

**Keywords:** radiation recall, breast cancer, dermatitis, radiation therapy, recall reaction, recall dermatitis

## Introduction

Radiation recall is a rare phenomenon wherein an acute inflammatory reaction confined to previously irradiated tissues occurs with exposure to a new inciting agent administered after completion of radiation therapy. This phenomenon can occur months to years after radiation exposure. A recall reaction presenting as a dermatitis is the reaction most commonly reported in the literature [1], but it can affect other organ systems such as respiratory or gastrointestinal systems [2]. The most frequently cited offending agents are systemic treatments such as chemotherapeutics or antibiotics. Hypotheses exist for drug-induced radiation recall, including vascular damage, epithelial stem cell damage, sensitivity, and drug hypersensitivity [1, 3]. Few, if any, hypotheses exist for ionizing radiation as a trigger of radiation recall. Here we report a case of radiation recall dermatitis occurring after a second course of radiation therapy in the absence of clinically significant overlap of the radiation fields.

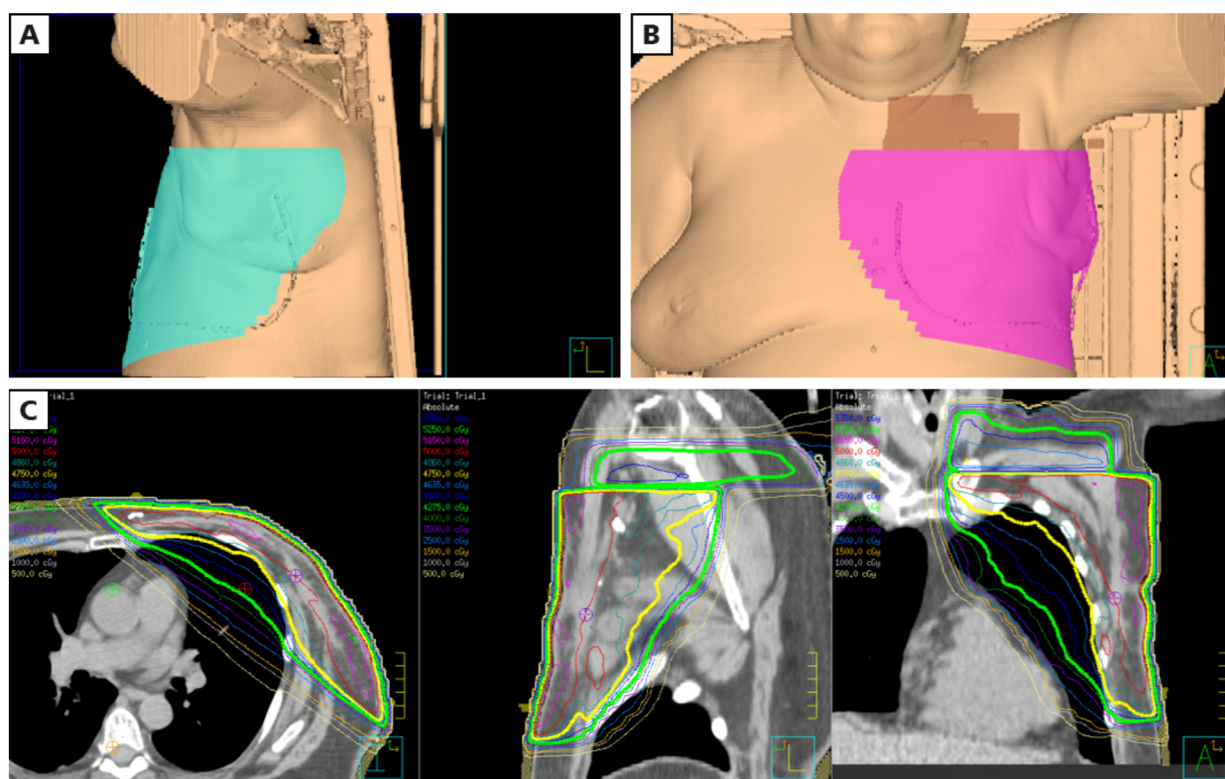
## Case presentation

A 63-year-old female with low-burden metastatic triple-negative breast cancer presented with pain and erythema of the previously irradiated left chest wall while undergoing high-dose palliative radiation therapy to a right lung nodule with ipsilateral hilar and mediastinal recurrence, without intervening systemic therapy.

Two years earlier, the patient presented with left-sided inflammatory triple-negative breast cancer (cT4b N1 M0). She completed four cycles of neoadjuvant dose-dense adriamycin and cyclophosphamide chemotherapy and one cycle of paclitaxel that was subsequently discontinued due to poor tolerance. She underwent a left-sided modified radical mastectomy (ypT1b ypN0, clear margins) complicated by an infected seroma and recurrent episodes of cellulitis requiring drainage and intravenous antibiotics. After resolution of her infection, she completed adjuvant radiotherapy to the left chest wall and regional lymph nodes. The radiation was planned using 6 and 18 MV photon beams and a four-field technique: modified wide tangent pair to the chest wall and internal mammary nodes up to 50 Gy in 25 fractions, with a parallel opposed pair configuration to the supraclavicular and axillary nodal regions up to 45 Gy in 25 fractions (Fig. 1). Bolus on skin (5 mm) was utilized. She de-

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**Figure 1.** Adjuvant radiation therapy plan to the left chest wall and regional nodes. Lateral (A) and anterior (B) view of the radiation beams on 3D skin rendering. Representative axial, sagittal, and coronal (left to right) views (C) demonstrating isodose coverage of the left chest wall and regional nodes (yellow = 4750 cGy, green = 4275 cGy)

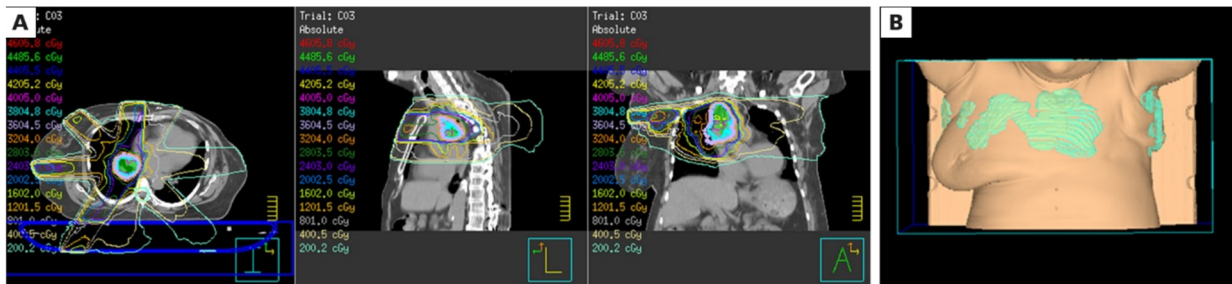
veloped acute moist desquamation of the left axilla as well as significant erythema with dry desquamation of the chest wall, requiring topical Flamazine ointment. The patient's radiation dermatitis completely resolved one month after the completion of her adjuvant radiation. However, following the patient's initial mastectomy, she suffered from ongoing chronic left chest wall pain. Her other relevant past medical history included complex pain syndrome on oral opioids, and potential ongoing undifferentiated connective tissue disease with ANA positivity (1:80) in the distant past as well as a patient-reported history of malar rash and arthritis. All repeat rheumatologic markers were subsequently negative.

After a disease-free interval of just under one year, the patient was, unfortunately, diagnosed with a histologically proven recurrence in a right lung nodule, right hilum, and paratracheal node. Chemotherapy was not offered at that time because of poor tolerance of her previous neoadjuvant breast cancer chemotherapy. The treating medical and radiation oncologists decided to offer the patient palliative radiation alone in an attempt to provide local disease control and delay time-to-chemotherapy. She was offered palliative radiation to a prescribed dose of 40 Gy in 15 fractions. The radiation was planned with 6 MV photons and intensity-modulated radiation therapy (IMRT) plan-

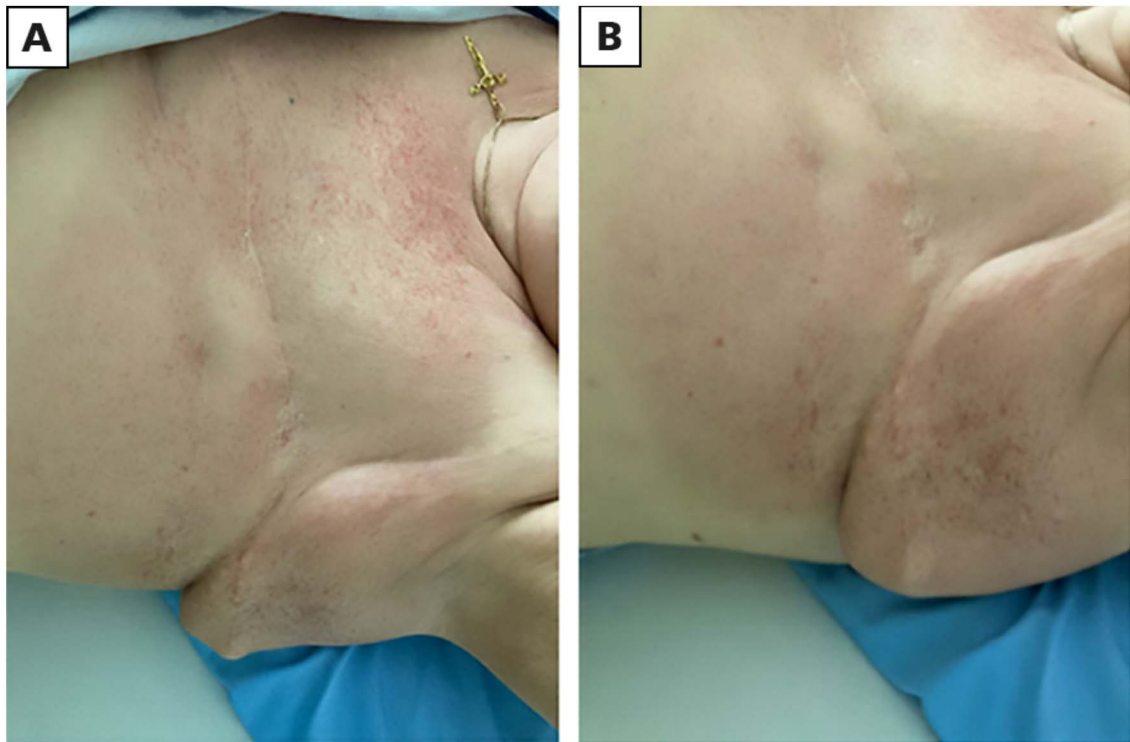
ning. Due to the nature of the IMRT plan, the previously irradiated chest wall was covered by the 5–10% isodose line (Fig. 2). Her palliative radiotherapy to the thorax was initiated approximately 13 months after completion of her adjuvant breast radiotherapy and 20 months after the completion of her neoadjuvant chemotherapy.

She had completed 6 out of 15 fractions before she was admitted to the hospital with left chest wall pain flare and a new rash. She presented with a two-day history of progressive erythema to the left chest wall causing acute worsening of her pain. On examination, the patient had a poorly demarcated patch of telangiectasia with mild underlying erythema. The borders of the erythema were confined to the previously irradiated chest wall field without significant induration, patch formation, or desquamation (Fig. 3). She had tenderness to palpation of the chest wall but no palpable nodularity or abnormal masses.

She denied taking any new medications other than topical lidocaine restarted for pain one week before the presentation, which she had used previously without side effects. She also denied undergoing any new skin exposures. Additionally, screening rheumatologic blood work for autoimmune or connective tissue diseases was repeated and found to be negative at symptom onset. She reported dyspnea which remained stable throughout her hospital stay and did not



**Figure 2.** Radiation therapy plan to the right lung and ipsilateral hilum/mediastinum; **A**, Axial, sagittal, and coronal (left to right) views demonstrating isodose coverage (teal = 200 cGy, tan = 400 cGy); **B**, Anterior view demonstrating the 5% isodose contribution (teal) to the left chest wall as seen on the 3D skin rendering



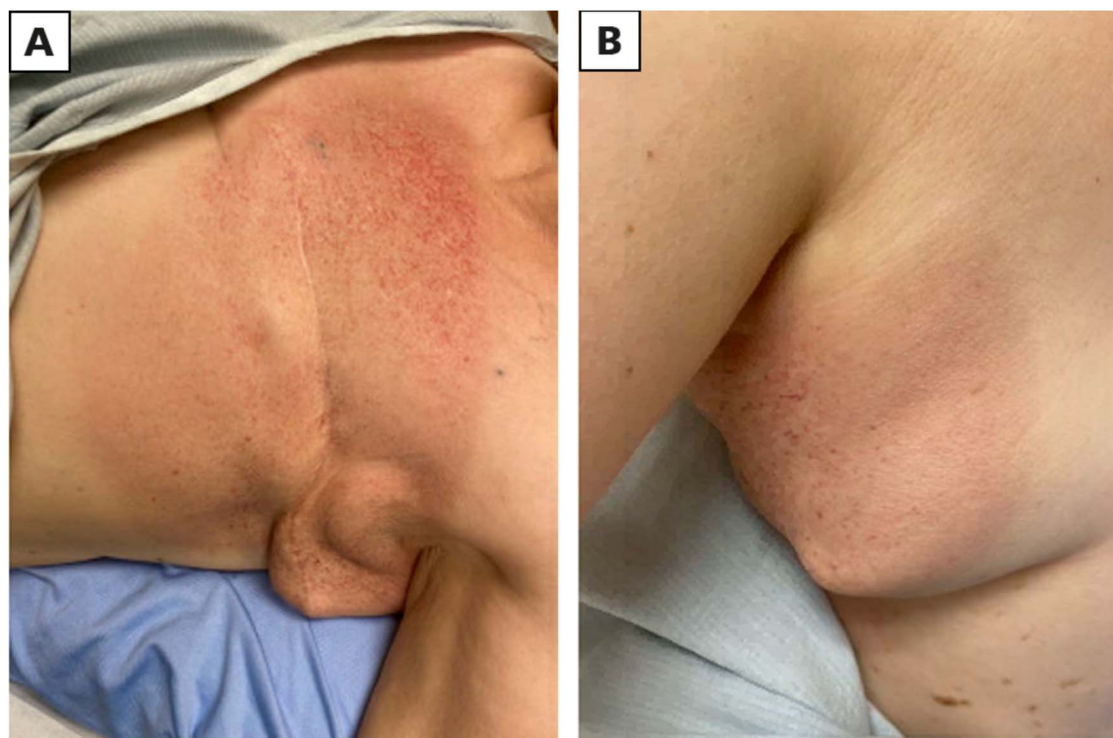
**Figure 3.** Erythematous reaction seen on the patient's left chest wall during irradiation to the right lung at 6/15 fractions. Anterior (**A**) and anterolateral (**B**) view of skin reaction

require supplemental oxygen therapy. Chest computed tomography (CT) on admission did not demonstrate any changes typical of pneumonitis.

Clinically, the patient was diagnosed with radiation recall dermatitis. Biopsy was not initially pursued because of the lack of nodules or other clear targets to sample. Rather, the patient and physician felt comfortable with close follow-up to ensure that there was no progression of the lesion causing concern for other differential diagnoses such as infection or skin metastasis. Topical lidocaine was continued, and dexamethasone 4 mg daily was initiated. Otherwise, conservative management of the skin was employed including skin care with moisturizing base cream and oral pain medications as needed.

After a discussion with the patient, she decided to continue thoracic radiation to completion. She did develop more erythema to the left chest wall as her thoracic radiotherapy progressed but did not develop any desquamation, nodules, or targets for biopsy (Fig. 4). There was no progression of her dyspnea, and no symptoms of acute esophagitis were noted on review.

The patient was re-assessed two months after completion of her thoracic radiation. She reported decreased chest wall pain, well controlled on oral hydromorphone. On examination, the chest wall was markedly less erythematous compared to the prior exam, with diffuse chest wall dryness noted. She continued to demonstrate late radiation change including telangiectasia (Fig. 5).



**Figure 4.** Erythematous reaction seen on the patient's left chest wall during irradiation to the right lung at 12/15 fractions. Erythema borders consistent with the patient's first radiation field to the left chest wall. Anterolateral (A) and posterior (B) view of skin reaction

## Discussion

To our knowledge, we describe the first documented case of radiation therapy-induced radiation recall reaction. A search was undertaken in the PubMed database, and no other radiation therapy-induced radiation recall cases were found [Tab. 1 for Medical Subject Headings (MeSH) terms]. Based on the patient's clinical history, there were no exposures or likely triggers for a radiation recall reaction including recent use of new oral medications or antineoplastic agents. The patient had had topical lidocaine administered one week before radiation recall dermatitis; however, after discontinuation, the radiation recall continued to worsen, making topical lidocaine unlikely to be the causative factor. Additionally, the patient had used the topical ointment previously without any reaction, and there have been no other documented cases of topical analgesics as a trigger of radiation recall dermatitis. Only after completion of radiation therapy did the skin reaction begin to subside.

Due to the nature of IMRT planning, there was low dose spread of the 5–10% isodose lines throughout the previously irradiated left chest wall, equal to approximately 2–4 Gy delivered over 15 daily fractions. This fractionated dose alone, even in the context of re-irradiation, would be unlikely to cause acute radiation dermatitis. The dose threshold for acute skin toxicity such as erythema generally lies around 20 Gy or



**Figure 5.** Anterior view of the erythematous reaction to the patient's left chest wall 2 months post-treatment of irradiation to the right lung

**Table 1.** Medical Subject Headings (MeSH) terms used for literature search for radiation recall literature

Search Terms		
Recall	AND	Radiation recall reaction
		Radiation recall dermatitis
		Radiation recall dermatitides
		Dermatitis, radiation recall
		Dermatitides, radiation recall

Within a column, OR terms were used

higher when delivered over 2 Gy fractions [4]. Moreover, the erythematous region encompassed the entire chest wall and did not follow the distribution of the low isodose bath (Fig. 2).

The patient had previously been investigated for undefined connective tissue disorder on multiple occasions, including by a rheumatologist. Each of these attempts yielded no definitive diagnosis with a remote ANA titer of 1:80, followed by negative rheumatological markers on subsequent testing. The tolerance of radiotherapy has been found to decrease for various connective tissue disorders for standard amounts of radiation to various sites, but not for spillage to low isodose areas [5, 6]. The dose of radiation received by the affected area was below the included range of dosages evaluated in those studies (< 10 Gy). It is less likely that a potential undiagnosed connective tissue disorder alone led to the dermatitis reaction observed in this patient. However, a possible underlying inflammatory condition and/or her history of a brisk radiation reaction in this region may have predisposed her to that intensified reaction.

While several theories for the mechanism of radiation recall reactions exist, the idiosyncratic hypersensitivity reaction theory appears to best explain the current clinical presentation. This theory proposed by Camidge and Price suggests that prior irradiation may result in changes to the local immune environment of the irradiated tissues and may lower the threshold for upregulation of cellular inflammatory mediators with introduction of an offending agent, commonly a drug [3]. In this way, exposure of previously irradiated tissues to even very low doses of irradiation, as seen in our patient, could result in clinically apparent reactions. Not entirely dissimilar to our case, there have been limited reports of radiation recall caused by local irritants such as ultraviolet (UV) light [7, 8] or ionizing radiation from diagnostic imaging [9], which would appear to support this theory.

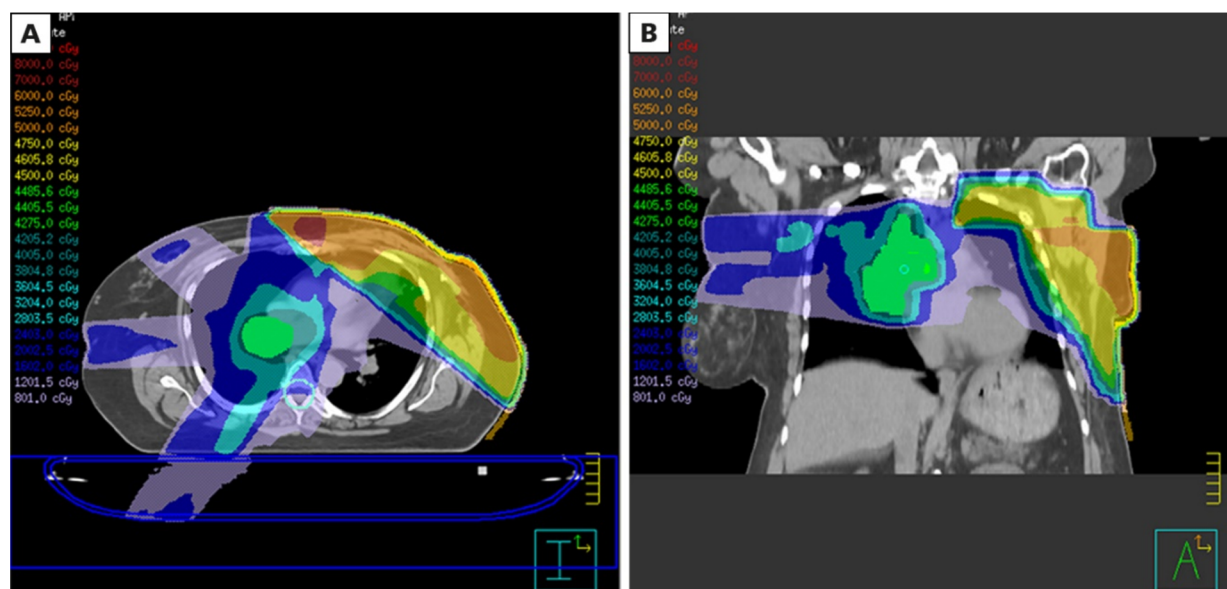
Camidge and Price also hypothesized that these local changes within the irradiated field may lower the threshold at which even systemic inflammatory reactions develop. In keeping with this theory, Del Guidice et al. [8] have described a case whereby sun exposure resulting in a sunburn in non-irradiated upper

extremities triggered an erythematous skin reaction in the region of the patient's buttocks during and again approximately one month after pelvic irradiation for prostate cancer. In that case, the buttock region was covered and not exposed to sunlight [8]. Similarly, this theory may explain the diffuse nature of our patient's chest wall erythema throughout the entire irradiated chest wall, which did not precisely correspond to the distribution of the low-dose region of the thoracic irradiation IMRT fields that overlapped with the prior field (Fig. 2).

The composite dose distribution for both breast and thoracic radiation plans did not identify significant volumes of cumulative radiation from both plans that would account for diffuse erythema in the left breast (Fig. 6). This composite plan is an estimate of the cumulative dose and is subject to some error secondary to setup differences in both treatments, including the use of deep inspiration breath hold and bolus on the skin for breast radiation, but not for thoracic radiation.

It is well-known that radiation therapy works by creating damage to DNA through direct damage to the phosphate backbone, as well as by indirect damage from the formation of reactive oxygen species (ROS) [10, 11]. Perhaps with subsequent exposures to radiation, either from excess sunlight, diagnostic imaging, or radiation therapy, ROS generation could trigger non-immune cell activation of the inflammatory response, similar to Camidge and Price's theory of hypersensitivity, which then cascades through the entire previously irradiated field. The range of energies emitted from diagnostic X-ray beams is on average up to 75 kV, creating ROS through a combination of the photoelectric electric effect and Compton effect, while therapeutic radiation acts largely through the Compton effect [12]. Although multiple mechanisms may contribute to ionizing radiation, ROS generation could be a link in the re-activation of inflammatory pathways leading to radiation recall reactions.

The timing of radiation recall reactions varies from months to years after completion of radiation therapy, with radiation recall dermatitis presenting even 25 years after radiation exposure in one reported case [13]. Recall reactions also affect many organ systems resulting in an array of presentations: pneumonitis [14], mucositis [15], myositis [16], colitis [17], etc. The potential for prolonged time intervals between radiation therapy completion and onset of recall reactions, the multitude of potential inciting agents (antineoplastic agents, antibiotics, UV light or ionizing radiation, and more recent reports of the COVID-19 vaccine), varying presentations, and the rarity of this phenomenon may complicate early identification and diagnosis. Moreover, while recall reactions may present as only mild symptoms such as grade 1 dermatitis, severe reactions such as



**Figure 6.** Composite plan of both the breast and thoracic radiation plans. Axial (A) and coronal (B) views. The two courses of radiation were separated by approximately 13 months. There was a small volume of tissue receiving > 7000 cGy cumulatively, but this area was minimal in comparison to the erythematous reaction seen in that patient

Stevens-Johnson syndrome [18, 19] have been reported. It is, therefore, critical that physicians are aware of the potential for radiation recall reactions to identify and manage them properly. Management may include conservative treatment, discontinuation of the causative agent, or even use of corticosteroids for severe cases.

## Conclusions

In this article, we have reported the first case of radiation therapy-induced radiation recall dermatitis. As patients are living longer after their cancer diagnosis, they are, therefore, more likely to undergo multiple treatment courses of chemotherapy or radiation therapy. Although rare, physicians should be aware of the possibility of radiation recall reactions during extended follow-up. While radiation recall reactions are most commonly reported after administration of cytotoxic chemotherapies or other oral medications, physicians should be aware of the possibility of radiation recall occurring with subsequent radiation courses, despite the absence of clinically significant overlap of the radiation fields, so that symptoms may be identified early and managed swiftly. It is not known whether all patients carry a similar risk or if this reaction is intensified by potentially predisposing factors such as a history of a brisk radiation reaction or a possible underlying inflammatory condition.

## Article Information and Declarations

### Ethics statement

The patient consented to being part of this study.

### Author contributions

I.K.: writing — original draft, review and editing; K.-K.D.Y.: conceptualization, data extraction, writing — original draft, review and editing; A.S.: writing — review and editing; J.L.: writing — review and editing; M.G.: conceptualization, data extraction, writing — original draft, review and editing, supervision.

All authors have read and agreed to the published version of the manuscript.

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### Conflict of interest

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### Supplementary material

None.

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