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Teaching Case

Case Report of a Woman With Anastrozole-Associated Radiation Recall

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Introduction

The treatment of breast cancer often involves the widespread use of radiation therapy (RT) in conjunction with chemotherapy. Both treatment modalities are associated with well-described, but not always overlapping, profiles of tolerability. Chemotherapy may be given after RT, and more so with recent studies showing benefits in individuals who do not receive a complete response with neoadjuvant treatment. However, this sequence can infrequently lead to the phenomenon of radiation recall.[1]

Radiation recall is a relatively rare and unpredictable occurrence, characterized by an acute inflammatory reaction localized to previously irradiated areas, triggered by the administration of certain systemic agents following RT.[2-5] These reactions can manifest as radiation recall dermatitis (RRD), encompassing a spectrum of effects ranging from maculopapular redness to vesicle formation and skin peeling.[2] The severity of these reactions varies, spanning from mild rashes to significant skin damage. Strikingly, these symptoms can emerge days or even years after radiation treatment, often within the previously irradiated region, despite minimal or no residual reaction from the initial RT. Reports have even shown permanent skin changes, including fibrosis, years after receiving RT.[6] Importantly, RRD may occur independently of acute skin reactions during RT, confounding the traditional understanding of radiation-related skin response. The incidence rate of RRD was reported as high as 8 in 91 cases in the palliative setting after chemotherapy.[7]

Traditionally, treatment involving radiation recall reactions is heavily dependent on the organ system involved. Radiation recall skin reactions are commonly treated with topical corticosteroids, along with termination of the therapy causing the reaction.[8] Antibiotic therapy is warranted if there is suspicion of a bacterial superinfection.

While anticancer agents are most commonly associated with radiation recall (Table 1),[9-33] it is essential to recognize that other drugs, including certain antibiotics, antituberculosis medications, and even cholesterol-lowering agents (such as simvastatin), can induce this phenomenon.[2,4] This diverse array of medications a patient may be taking while undergoing RT may confound the clinical significance of radiation recall. Notably, RRD has presented in breast cancer patients who were prescribed antimetabolite or taxane medications.[8] One such anticancer medication, anastrozole, known by its trade name Arimidex, is frequently used in the treatment of hormone receptor-positive breast cancer. It functions by blocking the conversion of androgens to estrogen by inhibiting aromatase, thus reducing estrogen production. In the majority of cases, patients are recommended to start anastrozole 2 to 6 weeks following completion of radiation.[34] Although it is a well-established treatment, instances of radiation recall linked to anastrozole are notably rare and sparingly documented in medical literature.[30]

In this case report, we discuss a unique situation where a breast cancer patient who had successfully completed

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Table 1 Anticancer agents associated with radiation call

Disease site	RRD treatment	Radiation dose	Drug caused RRD	Time to RRD	Reference
Breast cancer	Unspecified	30 Gy	5-Fluorouracil, (15 mg/kg daily for 4 d) 7 wk after RT	2 wk	Vonessen et al[9]
Breast cancer	Discontinued tamoxifen; resolved in 2 wk; rechallenged at 10 mg daily, with mild recurrence	Wide local excision and adjuvant RT	Tamoxifen (20 mg daily) started 2 y after RT	5 d	Parry[10]
Breast cancer	Antibiotics, chest wall debridement	61.5 Gy to the chest wall; 65.3 Gy to the supraclavicular region	Paclitaxel (130 mg/m^2 over 24 h), begun 2 d after RT	5 d	Raghavan et al[11]
Breast cancer	Discontinuation of paclitaxel	50 Gy to the breast; 54 Gy to the lymph nodes	Paclitaxel (175 mg/m^2 over 3 h), 13 mo after RT	5 d	Bokenmeyer et al[12]
Breast cancer	Healing within 10 d; treatment unspecified	50.4 Gy; mild skin erythema	Paclitaxel (200 mg/m^2) 7 d after RT	4 d	McCarty et al[13]
Breast cancer	Dose reduction; no recurrence of RRD	30 Gy to T10−L4 spine and pelvis	Docetaxel (100 mg/m^2) on a 3-weekly basis and prior oral dexamethasone (5 d) 4 d after a second injection	Within 7 d	Yeo et al[14]
Breast cancer	Local steroid cream, mometasone furoate for 10 d	54 Gy	Tamoxifen (20 mg/m^2 daily) 28 mo after RT	2 mo	Bostrom et al[15]
Breast cancer	Surgical debridement and microvascular free-flap reconstruction	Unspecified	Epirubicin	2 wk	Wilson et al[16]
Breast cancer	Docetaxel reduced to 75% and given 21 d later; steroids for 7 d	50 Gy	Docetaxel (100 mg/m^2) with dexamethasone (8 mg once daily for 3 d) 16 d after RT	Within 7 d	Camidge and Kunkler[17]
Breast cancer	Unspecified	Whole-brain irradiation: 2 Gy for 5 d weekly, up to 50 Gy	Docetaxel restarted (30 and 100 mg/m^2 weekly)	Unspecified	Giesel et al[18]
Breast cancer	Discontinuation of gemcitabine slowly resolved the skin reaction	30 Gy to lumbar spine	Gemcitabine (1000 mg/m^2 every 2 wk) + herceptin (weekly for 4 wk) 5.5 mo after RT	2 wk	Jeter et al[19]
Breast cancer	Methylprednisone (80 mg twice daily); docetaxel at 75% induced a less severe reaction	50.4 Gy + 10 Gy to tumor bed	Docetaxel (100 mg/m^2) + Decadron 10 d after RT	10 d	Morkas et al[20]
Breast cancer	Unspecified	30.9 Gy upper body irradiation + whole-brain and pelvis	Docetaxel (30 mg/m^2) 1 wk after RT	14 d	Piroth et al[21]
Breast cancer	Topical steroids (betamethasone dipropionate)	30 Gy to left femur	Pegylated liposomal doxorubicin (40 mg/m^2 on day 1 every 28 d) 4 wk after RT	12 d	Jimeno et al[22]

(*continued on next page*)

Table 1 (*Continued*)

Disease site	RRD treatment	Radiation dose	Drug caused RRD	Time to RRD	Reference
Breast cancer	Unspecified	50 Gy after modified mastectomy	Arsenic trioxide (0.15 mg/kg daily, 5 d/wk for 5 wk) second week of 3	Day 2 of wk 3	Keung et al[23]
Breast cancer	None; completely resolved 3 mo later	50.4 Gy + 10 Gy to tumor bed	Tamoxifen (20 mg daily)	3 mo	Singer et al[24]
Breast cancer	Oral methylprednisone led to 10-d remission	50 Gy + 10 Gy to tumor bed	Docetaxel (100 mg/m^2) 1 wk after RT	4 d after the second course	Borgia et al[25]
Breast cancer	None; resolved in 6 d; continued docetaxel with no recurrence	50 Gy + 10 Gy to tumor bed	Docetaxel (100 mg/m^2) + Decadron for 3 d 11 d after RT	Within 7 d	Kandemir et al[26]
Breast cancer	Prednisone 30 mg daily for 2 wk	50 Gy + 10 Gy to tumor bed	Phentermine 1 y after RT	Unspecified	Ash and Videtic[27]
Breast cancer	Oral cephalexin did not provide relief; tamoxifen was discontinued; diphenhydramine was given; restarted tamoxifen after 12 wk	50 Gy + 14 Gy to tumor bed	Tamoxifen (20 mg daily)	Within 1 wk	Kundranda and Daw[28]
Breast cancer	Topical corticosteroids during docetaxel therapy for 9 cycles	50 Gy in 20 fractions	Docetaxel (30 mg/m^2 weekly) restarted 14 d after RT	Day 6 after the second course	Mizumoto et al[29]
Breast cancer	Unspecified	50 Gy + 10 Gy boost to tumor bed	Anastrozole, 1 mg per day for a period of 5 y.	3 mo after RT	Haydaroglu et al[30]
Metastatic breast cancer	Unspecified	45 Gy to spine	Doxorubicin (Adriamycin: 80 mg/injection, 1 injection per month for 9 mo) given 7 y after RT	7 mo	Mayer et al[31]
Metastatic breast cancer	Topical therapy, nonsteroidal antiinflammatory; rechallenged with prednisone with mild recurrence	30 Gy to lumbar spine	Edatrexate (100 mg/m^2 biweekly), begun 6 wk after RT	After 3 doses (11 d)	Perez et al[32]
Metastatic breast cancer	Intravenous steroids for 2 d with minimal response	30 Gy; 25 Gy boost	Gemcitabine (1000 mg/m^2), 3.4 mo after RT	3 d	Jeter et al[19]
Metastatic breast cancer	Silver sulfadiazine cream and hydrocortisone eardrops; discolouration still apparent after 8 wk; started on cefuroxime with concurrent Decadron without recurrence	20 Gy (thoracic spine) + 20 Gy (whole brain)	Paclitaxel (175 mg/m^2) + gemcitabine (1000 mg/m^2) 1.5 wk after whole-brain radiation	2 d	Hird et al[33]

Abbreviations: RRD = radiation recall dermatitis; RT = radiation therapy.

RT developed radiation recall after starting anastrozole treatment. This case brings into focus the intricate interplay between RT and specific antineoplastic therapies, shedding light on the complexities of treatment. By sharing this case, our goal is to deepen our understanding of radiation recall and enhance its clinical management.

Case Description

Patient description: a 49-year-old female with a history of inflammatory arthritis presented with a diagnosis of stage 1A invasive mammary carcinoma of the left breast, pT1c pN0(sn)M0 G1, estrogen receptor (ER)+, progesterone receptor (PR)+, HER2−, and Oncotype DX score 10. She then received RT to a dose of 4256 cGy in 16 fractions prescribed to the entire left breast. She did not receive any boost radiation. She tolerated RT, with the only side effect being grade 1 dermatitis. Ten days following the completion of RT, the patient began treatment with anastrozole 1 mg by mouth daily. In the following 2 weeks, she noted the emergence of a rash in the inframammary fold (Fig. 1), which gradually worsened. Initial management included the application of a topical corticosteroid; however, this intervention failed to yield any improvement. The patient further reported the appearance of raised, erythematous lesions on the skin of the upper left breast. Triamcinolone ointment was subsequently prescribed, but it also proved ineffective in alleviating the rash. Around 28 days after taking anastrozole, the rash expanded to involve the entire breast, extended to the left axilla (Fig. 2), chest, upper abdomen, bilateral arms, lower back (Fig. 3), and into the hairline on the back of the head and neck (Fig. 4).

Notably, the rash transitioned from being painful to pruritic. In response to the worsening condition, the patient was administered Keflex (cephalosporin), a broad-spectrum antibiotic, 4 times daily to address any secondary bacterial skin infection. As the rash continued to progress and exhibited resistance to topical treatments, the decision was made to discontinue anastrozole, given its potential association with radiation recall. Following the discontinuation of Arimidex, the patient experienced a marked improvement in the rash after 16 days, and her symptoms subsided. Consequently, she transitioned to tamoxifen, an alternative hormonal therapy for breast cancer. There was no evidence of radiation recall to this agent, which she tolerated well and without issue.

Discussion

The case we presented underscores the imperative need to further our understanding of radiation recall in the context of breast cancer treatment. Radiation recall, characterized by infrequent and unpredictable acute inflammatory reactions within previously irradiated areas, can be incited by a wide range of medications. Despite its rarity, radiation recall has a substantial impact on patients' quality of life and treatment outcomes. Given the diverse array of medications capable of triggering this phenomenon, it deserves increased attention and the development of a comprehensive treatment approach. Our case report illustrates a breast cancer patient grappling with radiation recall induced by anastrozole treatment subsequent to RT, revealing the challenges inherent in identifying and implementing appropriate treatment interventions for this intricate reaction.

While radiation recall is conventionally associated with many medications, such as antimetabolite and taxane cancer drugs, its occurrence in conjunction with anastrozole represents a relatively uncommon event with limited representation in the medical literature. Thus, this case report extends the boundaries of our understanding of radiation recall, emphasizing its potential association with a broader spectrum of medications.

The complexities in addressing radiation recall are vast and further demonstrate the difficulty in identifying effective treatment. In past literature, topical corticosteroids were effective in treating radiation recall dermatologic reactions.[8] However, in this case, the initial interventions, including the use of topical corticosteroids and triamcinolone ointment, proved ineffective in alleviating the maculopapular rash. In fact, the rash not only remained but subsequently spread even during corticosteroid therapy. The widespread inflammatory response secondary to the initial RRD in this setting is less clear, as this phenomenon is poorly described in the literature. Morphea, an uncommon but notable side effect of RT, is a localized scleroderma-like reaction that results in skin thickening and hardening. This condition is often associated with underlying autoimmune disorders, which can predispose patients to its development.[35] Differentiating morphea from RRD is essential, as the latter typically presents as a more acute inflammatory response limited to previously irradiated areas following the administration of certain drugs. In contrast, morphea manifests gradually and is characterized by fibrotic changes rather than acute inflammation.[36] In this patient's case, a differential diagnosis was considered to distinguish between radiation recall and morphea. Clinical assessment, patient history, and the temporal relationship between drug administration and symptom onset were crucial in making this distinction, ultimately leading to a diagnosis of radiation recall.

It is unclear if her inflammatory arthritic medical condition or autoimmune disease may interact with radiation recall. This emphasizes the complexity of treating radiation recall, as different medications may present with similar symptoms, but some may be resistant to previously described management. In our case, the patient's dermatologic symptoms were not improved by corticosteroid therapy but rather by the discontinuation of anastrozole.

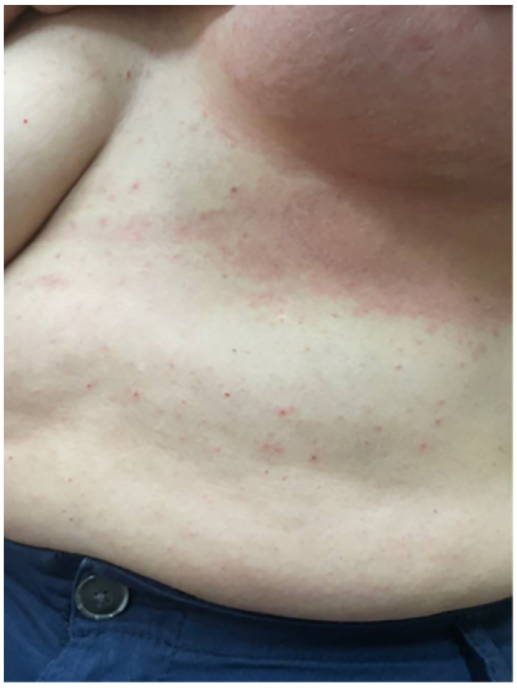

Figure 1 Initial inframammary fold rash 14 days after Arimidex starts.

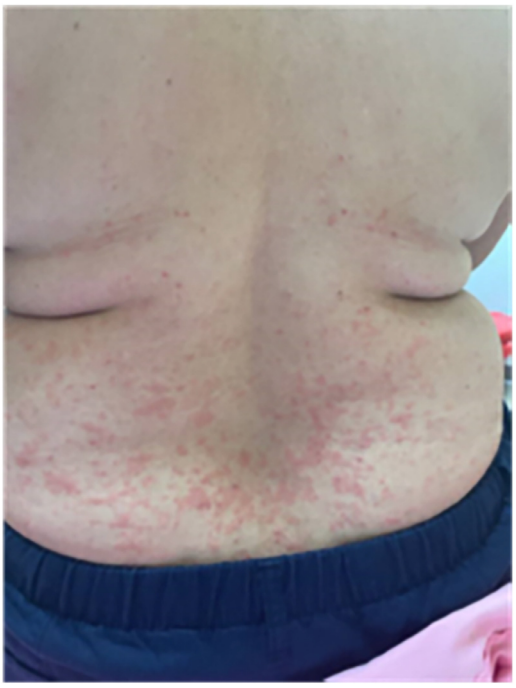

Figure 3 The lower back 28 days after Arimidex starts.

Though data are sparse, radiation recall may be underreported in patients with darker skin. The characteristic redness and inflammation associated with radiation recall may be less visible on darker skin tones, leading to potential underdiagnosis and underreporting in these populations. Recognizing this issue highlights the need for increased awareness and training among health care providers to identify and manage radiation recall effectively in all patients.

Recent literature underscores that radiation recall remains a poorly understood and unpredictable condition, with various chemotherapeutic agents, targeted therapies, and even immunotherapies implicated in its onset.[8] Unlike

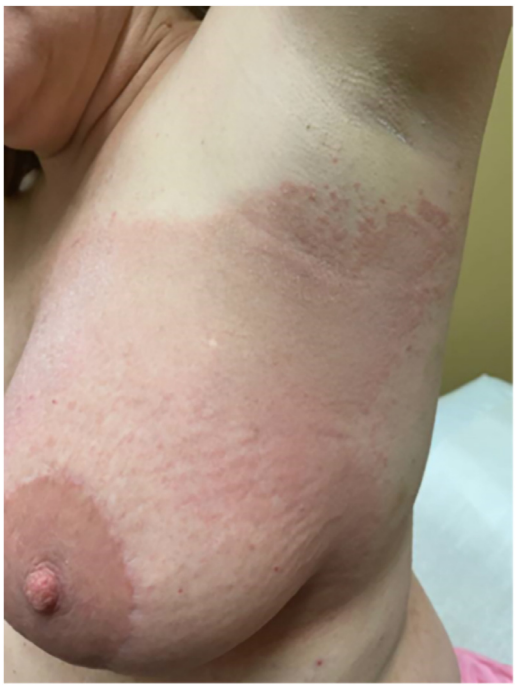

Figure 2 The rash involves the entire breast, extending to the left axilla at 28 days after Arimidex starts.

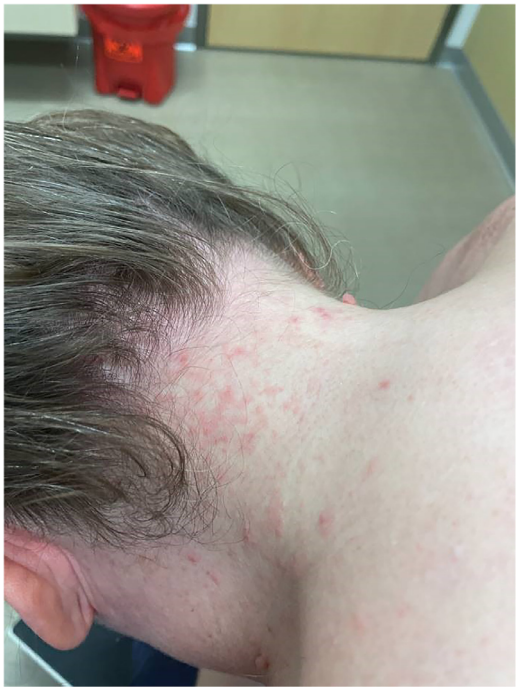

Figure 4 The hairline on the neck 28 days after Arimidex starts.

earlier reports, which predominantly advocate for the use of steroids to universally improve dermatitis,[37] contemporary reports indicate that this approach may not be effective for all patients, as evidenced by our case. Alternative management strategies, including discontinuation of the causative agent and the use of anti-inflammatory medications, are being explored. Furthermore, understanding the pathophysiological mechanisms, such as the role of immune modulation and genetic predisposition, could pave the way for more tailored and effective interventions. Hence, measures can be taken to separate treatments to minimize the risk of radiation recall reactions. However, this optimal time window is currently not defined to reduce such susceptibility to radiation recall.[7] Future research is needed to design cancer therapy timeframe guidelines.

Conclusions

This case report illustrates a rare occurrence of radiation recall secondary to anastrozole and highlights the need for an improved understanding of radiation recall and its management. The challenges our patient faced with ongoing lack of treatment success were largely attributable to the paucity of understanding of the nature of this phenomenon and the lack of standard clinical guidance for effective management strategies. This emphasizes the necessity for precautionary measures, further research, and clinical trials to enhance our understanding of radiation recall and identify methods to minimize the risk of adverse reactions.

Disclosures

Colin E. Champ receives income from books and lectures pertaining to nutrition and exercise and is on the Simply Good Foods Scientific Advisory Board.

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