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Tamoxifen-induced radiation recall dermatitis

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Abstract

Background: Radiation recall dermatitis (RRD) can present days to years after radiation exposure and is most commonly caused by chemotherapy drugs, with tamoxifen-induced radiation recall dermatitis being exceptionally rare. **Purpose:** To report a new case of tamoxifen-induced radiation recall dermatitis after 4.5 years of tamoxifen exposure, making this the longest time of onset to RRD after tamoxifen initiation. **Materials and Methods:** The case of a woman with tamoxifen-induced RRD is presented. Using PubMed and Google Scholar, the terms tamoxifen, radiation, recall, dermatitis were searched. Relevant citations were utilized and discussed. **Results:** An adult woman with history of inflammatory breast carcinoma developed an erythematous, scaly, tender plaque localized to previously irradiated skin of the left chest after more than four years of tamoxifen therapy. The patient was diagnosed with RRD and was treated with topical triamcinolone 0.1% cream twice daily to the affected areas. The patient experienced subsequent rapid improvement despite continuation of tamoxifen treatment. Biopsy revealed changes consistent with radiation dermatitis with no evidence of malignancy. **Conclusion:** Radiation recall dermatitis can have significant impact on affected patients and can pose a diagnostic dilemma for clinicians who may mistake RRD for infection or recurrence of malignancy. It is important to be familiar with the presenting signs and symptoms of this entity so that affected patients can receive timely and appropriate therapy.

Keywords: tamoxifen; radiation; recall; dermatitis

Introduction

Radiation recall dermatitis (RRD) is an acute inflammatory reaction at sites of previous irradiation after administration of a promoting agent. Recall reactions can occur in other areas of previous irradiation such as the lungs, bowel, esophagus, vaginal mucosa, laryngeal mucosa, and central nervous system, though the most common location is the skin [1]. The dermatitis can present days to years after radiation exposure [1-7]. Certain chemotherapy drugs such as anthracyclines (doxorubicin), taxanes (paclitaxel), and antimetabolites (gemcitabine) are most commonly associated with RRD, whereas it is less frequently associated with non-chemotherapy agents including antibiotics, statins, and anti-estrogenic medications such as tamoxifen [8-10]. Tamoxifen is a selective estrogen receptor modulator that works as an antagonist at estrogen receptors in breast tissue. It is used to treat and prevent recurrence of estrogen or progesterone receptor positive breast cancers. The overall prevalence of RRD is estimated at 8.8% with tamoxifen-induced RRD being exceedingly rare [11]. Herein, we report a new case of a 53-year-old woman with tamoxifen-induced RRD approximately 4.5 years after initiation of the drug. We go on to summarize the significant characteristics of all previously published cases and outline other common causes of RRD.

Case Synopsis

A 53-year-old woman with a history of inflammatory carcinoma of the left breast status post mastectomy and radiation therapy presented with a new rash on her chest. Concerning her past medical history, she was diagnosed with inflammatory carcinoma

in January 2011 and underwent chemotherapy with doxorubicin, docetaxel, carboplatin, and pegfilgrastim from January to June. Three weeks after completing chemotherapy she underwent a mastectomy and subsequent radiation therapy to the left chest wall and regional nodes for a total dose of 4539cGy. She experienced mild skin inflammation while receiving radiation. Several subsequent reconstructions were performed with skin grafting in January 2012. The patient began taking tamoxifen 10mg BID in July 2011. Other home medications consisted of venlafaxine, ibuprofen, esomeprazole, and vitamin B12.

In December of 2015, the patient presented with redness, irritation, burning, pain, and a stinging sensation affecting the left chest that developed gradually over several days. The symptoms were localized specifically to the skin of the left breast, chest, and left anterior arm. Physical exam revealed erythematous, indurated, scaly plaques confined to areas of prior irradiation (**Figure 1**). Of note, the skin graft used in reconstruction of the left breast after radiation was spared. Owing to the long latent period between tamoxifen initiation and dermatitis development, the spared skin graft site was a key finding in formulating a clinical diagnosis. Based on the patient's history and clinical findings, the diagnosis of RRD was made, likely secondary to tamoxifen as the additional medications she was taking at the time of presentation have not been associated with RRD. The patient was treated with topical triamcinolone 0.1% cream twice a day to the affected areas. After treatment was initiated, punch biopsy of skin of the left chest was obtained to rule out recurrence of her inflammatory breast carcinoma. Biopsy revealed sclerosis, dilated dermal vessels, and atypical fibroblasts consistent with radiation dermatitis with no evidence of malignancy (**Figure 2**). Since inflammatory carcinoma of the breast is known to have a high rate of recurrence, the patient continued tamoxifen treatment and experienced subsequent rapid improvement in symptoms with topical therapy alone.

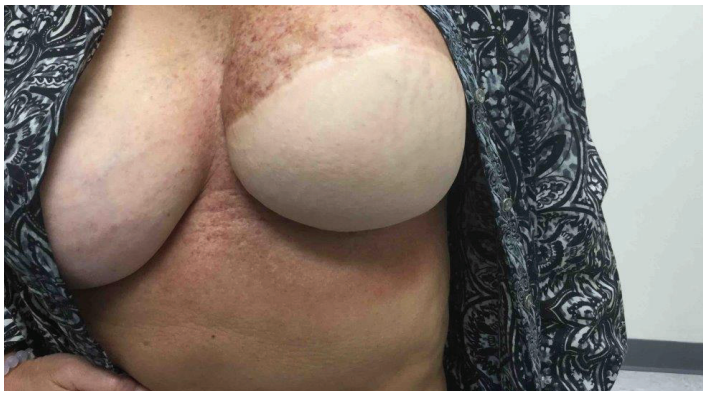

Figure 1. *Erythematous, indurated, scaly plaque involving the left breast, chest and left anterior upper arm.*

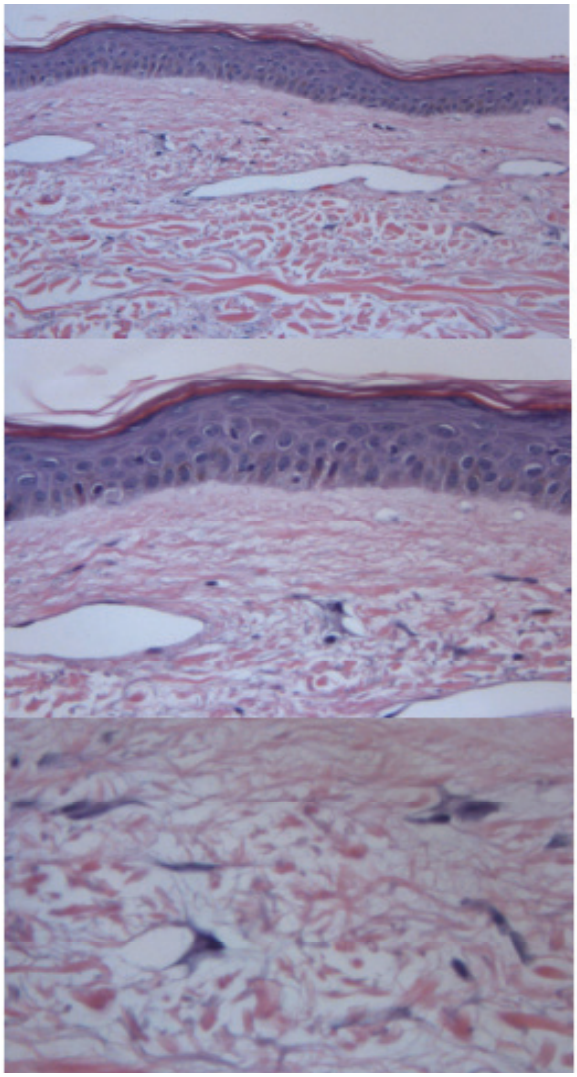

Figure 2. *(Top) At 20x, epidermal atrophy, telangiectasias with prominent endothelial cells and atypical pleomorphic fibroblasts. (Middle) Epidermal atrophy, telangiectasias with prominent endothelial cells and atypical pleomorphic fibroblasts. 40x. (Bottom) Numerous atypical pleomorphic fibroblasts can be seen on high power view. 63x.*

Case Discussion

The pathogenesis of RRD is poorly understood and

several mechanisms have been proposed. Theories of vascular damage, epithelial stem cell depletion, epithelial stem cell sensitization, and an idiosyncratic drug hypersensitivity reaction have been proposed as possible mechanisms of RRD [6,10,12-14].

Because the pathophysiology of RRD is not well understood, clinical diagnosis is based on patient history, symptoms, physical exam findings, and lab work to exclude other causes of dermatitis. The history is the most important feature of the diagnosis as the physician has to establish past exposure to radiation, define specific fields of radiation, and identify an inciting agent based on association and timing. The time frame for RRD occurrence varies greatly ranging from days to years after radiation therapy [1-7]. Any dermatitis occurring during radiation therapy must completely resolve before a diagnosis of RRD can be considered. It has been suggested that skin reactions from drugs given less than 7 days after radiotherapy should be considered radiosensitization as opposed to RRD [10]. Although there is no consensus on the average length of time between initiation of an offending drug and development of RRD, RRD usually occurs within a couple of weeks after initiation of treatment [10,15]. Based on previously reported cases of tamoxifen-induced RRD, time of onset can range from 5 days to 22 months after exposure to tamoxifen (**Table 1**) [2-7]. The case presented here involved an onset of RRD greater than four years after initiation of the promoting medication. This represents the longest reported time interval to onset of RRD related to tamoxifen.

On physical exam, RRD appears as a painful erythematous, edematous, and urticarial-like rash that can be accompanied by vesiculation, dry desquamation, hemorrhage, and ulceration [1-7,10]. Camidge and Price proposed a grading system for the RRD (**Table 2**) [10]. The patient presented here had similar symptomology and would be classified as a grade 1. Diagnosis of tamoxifen-induced RRD in past reports have required certain clinical findings such as localized inflammatory skin reactions corresponding to site of prior irradiation, development of symptoms during tamoxifen treatment, and exclusion of other medications as the cause of RRD [2-4,6,7].

As there are no particular tests used to diagnose RRD, however, lab work may be helpful to exclude other possible diagnoses such as infection. Histologically, skin biopsies have shown nonspecific changes and therefore are generally not recommended for diagnosis of RRD [1,6,10,15].

Table 1: *Cases of tamoxifen-induced RRD*

Age	Radiation Dose	Time from RT to tamoxifen	Time to onset of RRD	Treatment	Recovery time from RRD	Recurrence	Reference
47	50.4 Gy plus 10 Gy to tumor bed	Began tamoxifen & RT at same time	22 months	Continued tamoxifen, antibiotics	1 week	Yes	[2]
48	54 Gy	3 years	2 months	Cessation of tamoxifen and inititation of toremifene, antibiotics, topical steroids	7 weeks	No	[6]
48	50 Gy and 14 Gy to tumor bed	unknown	1 week	Cessation of tamoxifen, antibiotics, antihistamine	Few weeks	Yes, upon rechallenge of tamoxifen	[7]
52	50 Gy and 10 Gy	2 months	3 weeks	Continued tamoxifen, oral corticosteroid, antihistamine	Unknown	unknown	[5]
53	45.4 Gy	1 month	4.5 years	Continued tamoxifen, topical steroids	Few weeks	No	
70	Unknown	2 years	5 days	Cessation of tamoxifen	2 weeks	Yes, upon rechallange of tamoxifen	[3]
88	50.4 Gy and 10 Gy to tumor bed	2 years	3 months	Continued tamoxifen, antibiotics	1 month	No	[4]

Table 2: *Grading Scale for RRD*

Grade	Clinical signs
Grade 1 (mild)	Erythema +/- pruritus +/- dry desquamation
Grade 2 (mild-moderate)	Grade 1 with pain, edema, urticarial, or vesiculation
Grade 3 (moderate)	Moist desquamation
Grade 4 (severe)	Necrosis, ulceration or hemorrhage

Table 3: *Drugs causing RRD*

Drug	Reference
5-fluorouracil	[20]
arsenic trioxide	[21]
bleomycin	[19]
capecitabine	[22]
cefotetan	[23]
cyclophosphamide	[24]
dacarbazine	[25]
dactinomycin	[16]
docetaxel	[26]
doxorubicin	[9]
edatrexate	[27]
gatifloxacin	[28]
gemcitabine	[8]
hydroxyurea	[18]
interferon alfa-2b	[29]
levofloxacin	[30]
methotrexate	[31]
oxaliplatin	[32]
paclitaxel	[33]
pemetrexed	[34]
simvastatin	[14]
tamoxifen	[2]
trastuzumab	[35]
trimetrexate	[36]
vinblastine	[17]

Primary treatment of RRD is discontinuation of the offending agent (**Table 3** illustrates most commmon drugs causing RRD). However, this poses a problem for patients who have no other treatment options [3,6,7].

Systemic corticosteroids have also been used to prevent recurrence of symptoms when restarting a promoting drug after temporary cessation [5,6]. Prior cases of tamoxifen induced RRD have been treated with cessation of tamoxifen and use of local topical steroids. Spontaneous recovery from RRD while continuing tamoxifen has been reported in some cases [2,4,5]. The time from onset of RRD to improvement of dermatitis varies from weeks to months and does not appear to be treatment dependent [2-7,10]. Antibiotics are not indicated in most cases of RRD, but have been prescribed empirically if cellulitis or mastitis is suspected.

Conclusion

Radiation recall dermatitis can have significant impact on affected patients and can pose a diagnostic dilemma for clinicians who may mistake RRD for infection or recurrence of malignancy. Certain drugs have been commonly association with RRD. However, there are only a few published cases of tamoxifen-induced RRD (**Table 1**) [2,8,9,14,16-36]. Typically it presents as an erythematous, edematous, urticarial-like rash with desquamation, vesiculation, and ulceration. Diagnosis is based on patient history, symptoms, physical exam findings, and lab work to exclude other causes of dermatitis. Treatment options have included discontinuation or continuation of the promoting drug, topical steroids, systemic steroids, antihistamines, and antibiotics. We present a case of RRD related to tamoxifen presenting greater than 4 years after tamoxifen initiation. This represents the longest interval between tamoxifen initiation and

onset of dermatitis. It is important to be familiar with the presenting signs and symptoms of this entity so that affected patients can receive timely and appropriate therapy.

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