Radiation recall dermatitis induced by tamoxifen during adjuvant breast cancer treatment

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Introduction

Radiation recall dermatitis (RRD) is an acute skin inflammatory reaction at previously irradiated sites that is induced by the administration of certain agents after radiotherapy [1]. Chemotherapeutic, non-chemotherapeutic agents and a few antibacterials have been reported to induce RRD [1]. Despite several hypotheses about the cause of RRD, its pathophysiology remains poorly understood [2]. Although one study reported that the overall RRD frequency was 8.8% (8/91) in patients that underwent palliative radiotherapy followed by chemotherapy, other studies have suggested a lower incidence (<6%) [1,3].

Tamoxifen and radiotherapy are used in breast cancer treatment worldwide. Tamoxifen-induced RRD, however, has been very rarely reported [4-7]. Therefore, we report a case of RRD induced by tamoxifen.

Case Report

A 47-year-old woman was diagnosed with cancer of the right breast in September 2011. The patient underwent quadrantectomy with axillary lymph node dissection. The histopathological analysis revealed a 2.1 x 2.0-cm invasive ductal carcinoma with no lymph node metastasis. The immunohistochemical assessment of the tumor was estrogen receptor (Allred score, 5) and progesterone receptor (Allred score, 9) positive. The human epidermal growth factor receptor 2 was negative as confirmed by fluorescence in situ hybridization. The patient was administered adjuvant treatment that included four cycles of doxorubicin and cyclophosphamide every 3 weeks, followed by tamoxifen and...
radiotherapy. The patient received 50.4 Gy to her entire right breast, and 10 Gy locally at the tumor site, over a period of 2 months (between January 17, 2012 and March 19, 2012). Tamoxifen (20 mg/day) was also administered to the patient on January 17, 2012.

In December 2013, the patient developed a heating sensation, tenderness, edema, and redness at the irradiated area of the right breast (Fig. 1A). The patient had taken an over-the-counter (OTC) drug for an upper respiratory infection on the previous day. The patient continued taking tamoxifen, and the symptoms subsided within 1 week. In approximately 3 weeks, however, the patient experienced a recurrence of the previous symptoms, the abrupt development of a heating sensation, mild tenderness, edema, and redness, in the same area of the right breast (Fig. 1B). The patient was only taking tamoxifen at this time. The physician empirically prescribed cephalosporins for 14 days under the suspicion of mastitis, despite no obvious signs of infection, no fever or chills, negative blood cultures, and normal C-reactive protein levels. The symptoms improved within 1 week. The patient continued tamoxifen administration.

**Discussion**

As a selective estrogen receptor modulator, tamoxifen reduces the recurrence and mortality from hormone receptor (HR)-positive early breast cancer; it is used worldwide as a standard endocrine therapy for HR-positive breast cancer [8]. Tamoxifen-induced RRD has been reported in only four cases since it was first reported in 1992 [4-7]. In prior reports, the patients were diagnosed with tamoxifen-induced RRD based on the following clinical findings: 1) localized symptoms of an acute inflammatory skin reaction at previously irradiated areas, 2) symptom development during tamoxifen treatment, 3) no other therapy provoking RRD, and 4) negative test results for infection and/or breast cancer recurrence or other malignancy [4-7].

Previous studies reported that RRD occurred 5 days to 3 months after tamoxifen administration [4-7]. In two of four reported cases, the symptoms improved in 2 or more weeks after stopping tamoxifen administration. Tamoxifen was administered again to the two patients. They experienced a mild skin reaction only [4,6]. The third patient continued tamoxifen during RRD. In this case, the inflammation decreased after 1 months and the affected area completely healed within 3 months [5]. In the case of the last patient, the symptoms gradually improved 7 weeks after stopping tamoxifen; subsequently toremifene was administered [7] (Table 1).

The patient in our study also experienced localized acute inflammatory symptoms in the irradiated area of her right breast without evidence of infection during tamoxifen treatment. The possibility of breast cancer recurrence was excluded due to spontaneous resolving of skin lesion without a change in treatment. Although the patient had taken an OTC drug once prior to the first event, she didn’t have any medications except for tamoxifen before the second event. In Korea, an OTC drug does not contain antibiotics, and the patient took antibiotics after her symptoms recurred. Consequently, we excluded the possibility that the antibiotics were the cause of the recurrent RRD in this patient. Additionally, tamoxifen was the only medicine that could have induced recurrent RRD. The patient continued the tamoxifen because we did not realize that the cause of dermatitis was radiation recall phenomenon.
and it could be induced by tamoxifen. However, despite
continuing the tamoxifen, the mechanism of spontaneous
recovery from RRD in both a previously reported case and in
ours is unknown. If we had taken a tissue biopsy from the
lesion, it could have helped elucidate the mechanism of this
phenomenon.

Until now, guidelines have not existed for diagnosis
and treatment of RRD, or for re-challenging patients with
precipitating agents [1,9]. Previously proposed hypotheses
of pathophysiology vary between depletion and/or impaired
function of epithelial stem cells, changes in stem cell
sensitivity, vascular permeability or proliferative changes,
cumulative direct DNA damage and oxidative stress, the
Koebner phenomenon, idiosyncratic drug hypersensitivity
reactions, and effects of cytokine and mast cells [7,9-16].
However, because these abovementioned hypotheses lack
supporting studies and a clinical diagnosis based on signs,
symptoms, laboratory findings (to exclude infection and
malignancy), and a history of medication and radiation therapy
in our case, the time to RRD onset after tamoxifen
administration was 22 months, which is the longest time
interval among reported cases of tamoxifen-induced RRD.
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administration was 22 months, which is the longest time
interval among reported cases of tamoxifen-induced RRD.
In conclusion, a better understanding of the pathophysiology
of RRD will result in a definite diagnosis without ambiguity
using laboratory methods. RRD, radiation recall dermatitis.

Re-challenging or continuing tamoxifen in premenopausal HR-positive breast cancer patients with mild to moderate degree RRD could be induced by tamoxifen. However, despite continuing the tamoxifen, the mechanism of spontaneous recovery from RRD in both a previously reported case and in
ours is unknown. If we had taken a tissue biopsy from the
lesion, it could have helped elucidate the mechanism of this
phenomenon.

Conflicts of Interest

No conflict of interest relevant to this article was reported.

Table 1. Published cases of tamoxifen-induced RRD

| Reference | Age (yr) | Radiation dose | Time interval between radiation and tamoxifen (yr) | Tamoxifen dose (mg/day) | Time to onset of RRD (days) | RRD treatment | Time interval between onset and improvement of RRD (weeks) | Re-challenge of tamoxifen |
|-----------|---------|----------------|---------------------------------------------------|------------------------|-----------------------------|---------------|----------------------------------------------------------|--------------------------|
| Parry [4] | 70      | Unknown dose to the right breast | 2 | 20 | 5 days | Cessation of tamoxifen | 2 weeks after cessation of tamoxifen | Yes |
| Bostrom et al. [7] | 48 | 54 Gy to the left breast | 3 | 20 | 2 months | Antibiotics, local steroid cream, and cessation of tamoxifen | 7 weeks after cessation of tamoxifen | No: toremifene |
| Singer et al. [5] | 88 | 50.4 Gy to the left breast and 10 Gy boost to the tumor bed | 2 | 20 | 3 months | Antibiotics | 1 month after continuously taking tamoxifen | Yes: continuously taking tamoxifen |
| Kundranda and Daw [6] | 48 | 50 Gy to the right whole breast and 14 Gy to the tumor bed | Unknown | 20 | 1 week | Antibiotics, cessation of tamoxifen, and antihistamine | Gradually over the next few weeks | Yes |

RRD, radiation recall dermatitis.
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