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RADIATION RECALL DERMATITIS INDUCED BY TAMOXIFEN

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Abstract: ***Introduction:*** *Radiation recall dermatitis is an inflammatory skin reaction that occurs in a previously irradiated body part subsequent to drug administration especially chemotherapy.*
Clinical case*: A 52-year-old woman was diagnosed with invasive ductal carcinoma of the left breast in May 2008. She initially received neoadjuvant chemotherapy with doxorubicin and cyclophosphamide in a 4 series. In October 2008 was performed left sectorectomy with axillary lymphadenectomy followed again by chemotherapy with doxorubicin and cyclophosphamide. In the period January to February 2009 the patient received radiotherapy with 50 Gy in 20 fractions and an additional dose of 10 Gy in 5 fractions on the area of the axillary lymphadenectomy. A therapy with 20 mg/day tamoxifen was commenced in April 2009. Three weeks after the therapy with tamoxifen was started, a localized pruriginous erythematous lesion occurs in previously irradiated area. Treatment with topical corticosteroids and oral antihistamines led to partial resolution of radiation recall dermatitis allowing the continuation of tamoxifen.*
Discussion*: Radiation recall dermatitis may occur after several minutes or days from administration of medication and from days to years after exposure to ionizing radiation. The precise mechanism of action for radiation recall dermatitis is yet not known, it is considered either a idiosyncratic drug hypersensitivity reaction, or an increase of activity of some cytokines (IL-1, IL-6, TNF, TGF) released by radiotherapy when the medication was introduced.*
Conclusion*: Radiation recall dermatitis should be suspected in the patients that develop inflammatory reaction on previously irradiated areas.*

Key words: *dermatitis, radiotherapy, chemotherapy.*

1. Introduction

Radiation recall, also called radiation recall dermatitis (RRD), refers to the appearance of localized cutaneous inflammatory phenomena limited to a previously irradiated area, after administration of certain medications. RRD may occur days or years after irradiation [22], most often being associated with the use of chemotherapy. Depending on the severity, RRD clinically presents as erythema, necrosis, ulceration or bleeding.
Although the phenomenon is well known in the medical world, the exact cause remains unknown. We present the case of a patient with breast cancer who presented RRD to tamoxifen after radiotherapy.

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2. Clinical case

A 52 year old patient was diagnosed in 2008 with invasive ductal carcinoma of the left breast. The patient initially performed neoadjuvant chemotherapy in 4 series of doxorubicin and cyclophosphamide. In October 2008 left mammary sectorectomy and left axillary lymphadenectomy were performed followed again by chemotherapy with doxorubicin and cyclophosphamide. During January-February 2009 the patient followed radiotherapy 50 Gy fractionated in 20 series plus additional 10 Gy fractionated in 5 series on axillary lymphadenectomy area. Since April 2009 she began treatment with tamoxifen 20 mg/day. 3 weeks after she starting tamoxifen, it was found the appearance of a pruriginous erythematous plaque located on previously irradiated area (fig. 1 and 2). Orally treatment with corticosteroid and antihistamines resulted in partial remission of RRD allowing continuation of tamoxifen.

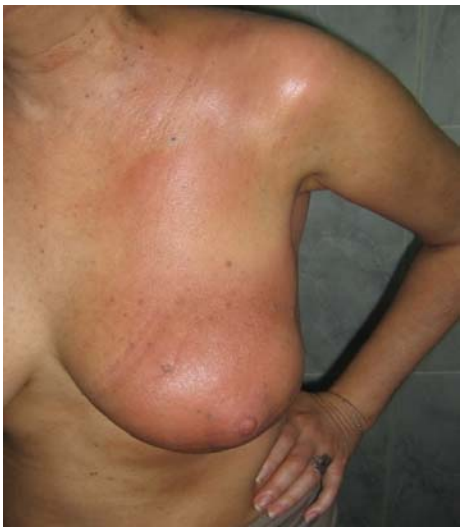

Fig. 1. *Erythematous, pruritic plaque located on previously irradiated area (anterior aspect)*

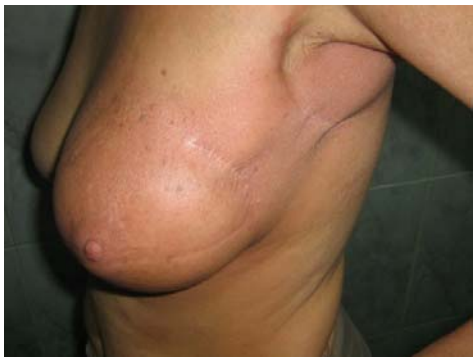

Fig. 2. *Erythematous, pruritic plaque located on previously irradiated area (lateral aspect)*

3. Discussion

Radiation recall, also called radiation recall dermatitis (RRD) is defined as the recurrence of cutaneous inflammatory phenomena on previously irradiated skin area in response to a series of cytotoxic medications.

RRD was published and documented for the first time by D'Angio et al. [11] in 1959, and the inducer drug of these abnormal reactions was dactinomycin. Clinical, RRD may present varying degrees of severity from erythema to necrosis, ulceration or bleeding. Severe RRD tend to occur when inducing medication, usually a cytostatic, is introduced shortly after discontinuation of radiotherapy, but there is no a certain level of radiation to produce this reaction.

RRD may occur after administration of various medications: doxorubicin [4,8], actinomicin D [12], methotrexate [10], paclitaxel [2], etoposide [14], gemcitabine [5], bleomycin [25], simvastatin [1], docetaxel [6], fluorouracil [27], hydroxyurea [24], tamoxifen [3],[21], and vinblastine [20]. Also were published cases of RRD occurred after administration of interferon alfa-2b [26], tuberculostatics [13] or antibiotics: cefazolin [16], ciprofloxacin, tobramycin and piperacillin [19]. RRD appears after minutes or days from the administration of inducing drug

and after weeks or months following the end of radiotherapy. In our case RRD occurred 3 weeks after administration of tamoxifen and 9 weeks after radiotherapy. The great majority of RRD seem to occur when radiotherapy and chemotherapy are separated by a period of less than two months. RRD usually occurs at the first administration of inducing drug [22], but there is also the possibility to administer the same drug without producing RRD [25], [28]. RRD usually recurs at administration of the same drug. Intravenous medications seem to induce faster RRD than orally administered medications. The time of disappearance of the dermatitis also differ depending on the way of administration of medication, in a few weeks after intravenous administration and within a few months after administration per os [3]. The difference was due to different pharmacokinetic of drugs depending on the route of administration. Although the common location of RRD is on the skin, were also published other locations such as lung [23], esophagus [18], oral mucosa and vaginal mucosa [15].

The pathogenesis of RRD remains unclear. Vascular damage, impairment of epithelial function of stem cell by irradiation, direct damage of DNA by cumulative effect of irradiation and oxidative stress, have been incriminated [17]. The fact that non-cytotoxic medications may induce RRD have made Camidge [7] to speculate that it could be an idiosyncratic hypersensitivity reaction to drug. Camidge also suggested that "trauma" on the previously irradiated skin would induce immune responses with little or no systemic activation, similar to Koebner phenomenon [7]. Another possible involved mechanism could be induction release of certain cytokines by radiotherapy such as interleukin-1 (IL-1), interleukin-6 (IL-6), platelet-derived growth factor-beta (PDGF-β), tumor necrosis factor (TNF) and transforming growth factor (TGF) responsible for an inflammatory response. After irradiation cells continue to secrete low levels of cytokines and, when entering inducing medications these cytokines increase their activity causing skin reaction.

Although it is rare, RRD can make impossible the use of some medications in a series of serious conditions and can endanger the lives of these patients. The role of topical or systemic corticotherapy, mast cell inhibitors and antihistamines in preventing RRD is debatable.

RRD treatment is mainly based on inducing medication discontinuation. Dexamethasone administered orally [9] or topics with hydrocortisone [25] have proved effective with lesions disappearance in 7-10 days. In other cases, the lesions disappeared spontaneously after discontinuation of medication without the use of antihistamines or corticosteroids [1], [12], [28].

4. Conclusion

Radiation recall dermatitis should be suspected in patients with inflammatory phenomena in a previously irradiated area shortly after the administration of certain medications, including tamoxifen. Rapid recognition of this phenomenon allows an appropriate treatment.

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