Teaching Case

Koebner phenomenon: Consideration when choosing fractionation for breast irradiation

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Received 10 October 2017; accepted 21 November 2017

Case report

A 62-year-old woman with a remote medical history of psoriasis initially presented with a palpable right breast mass. She underwent right breast ultrasound that revealed a hypoechoic mass at 10:30, 6 cm from the nipple, that measured 1.7 × 2.1 × 2.1 cm. Biopsy of the mass revealed invasive ductal carcinoma. Subsequent breast magnetic resonance imaging scans confirmed the right breast cancer, but also revealed a suspicious left breast region at 1:00. Biopsy of the left breast mass revealed a radial scar.

The patient was evaluated by both breast and plastic surgery physicians and subsequently underwent right partial mastectomy and sentinel lymph node biopsy and excisional biopsy for the radial scar followed by bilateral oncoplastic breast reduction. Final pathology showed right breast multifocal invasive ductal carcinoma, grade 3, with no involved sentinel nodes, and left breast ductal carcinoma in situ. The patient’s postoperative course was complicated by bilateral seromas requiring drainage as well as bilateral breast cellulitis treated with antibiotics. She was evaluated by the radiation oncology department, and the decision was made to delay starting radiation to allow adequate wound healing. In the interim, she was started on Anastrazole 1 mg. The patient was assessed weekly, and eventually radiation was begun on the right breast, with the left side delayed to allow for further healing.

The patient was treated in the prone position with hypofractionated whole breast radiation therapy (WBRT) of 42.56 Gy in 16 fractions with a 10 Gy boost to the right breast starting November 21. She completed treatment on December 21 without treatment breaks. During the second week of treatment, using daily Hydrophor and topical hydrocortisone as needed, the patient developed grade 1 erythema and pruritus of the right breast. After her left-sided seroma drainage resolved, she started adjuvant hypofractionated WBRT of 42.56 Gy in 16 fractions to the left breast on January 5, which she completed on January 27 without treatment breaks. During the second week of treatment, the patient developed grade 1 erythema of the left breast. Her right breast erythema improved with mild hyperpigmentation.

The patient was seen for routine follow-up on March 1 approximately 1 month after completing her left breast radiation course. The patient noted that the erythema in her left breast was resolving (Fig 1a); however, over the course of the following few days, she noted a new rash on her right breast (Fig 2a) in the distribution of her radiation field (Fig 2b), along with similar rashes in her right inguinal region (Fig 1b) and her left wrist. The patient’s psoriasis had been inactive for more than 5 years. She was seen by her dermatologist, who suspected Koebner phenomenon. The patient underwent biopsy of the right inguinal rash;
pathology demonstrated psoriasiform dermatitis consistent with psoriasis. She was started on a course of topical corticosteroids with complete resolution of her symptoms.

**Discussion**

In this case report, we describe an instance of Koebner phenomenon in a patient with a distant history of active psoriasis who received sequential bilateral hypofractioned WBRT. First described by Heinrich Koebner in 1876, the Koebner phenomenon (also known as isomorphic response) refers to the development of dermatologic lesions in otherwise healthy-appearing skin at sites of cutaneous injury. Although initially described as formation of psoriasiform lesions in previously normal-appearing skin of psoriatic patients after cutaneous trauma, the Koebner phenomenon is also known to occur in other skin diseases such as vitiligo, lichen planus, and bullous dermatoses. An “all-or-none” principle was shown with the Koebner phenomenon: If a patient responded to 1 type of stimulus, he or she would react to all. The response to trauma was further characterized into 4 outcomes: (1) maximum Koebner response, (ie, psoriasis to the entire trauma site), (2) minimal isomorphic response (ie, disease developing in some of the trauma site), (3) isomorphic abortive response (ie, self-limiting lesions resembling psoriasis beginning to appear but resolving in about 12 to 20 days), and (4) no psoriatic reaction. Various forms of cutaneous trauma have been reported to induce the Koebner phenomenon, including burns, friction, surgical incision, dermatoses, drug reactions, and irradiation. Typically, the timeline for isomorphic response is between 10 and 20 days, but it can range from 3 days to as long as 2 years. The exact mechanism for the Koebner phenomenon is unclear at this time, although multiple factors are postulated to play a role, including immune response, vascular changes, dermal and epidermal involvement, various growth factors, presence of neural cells within the skin, genetic predisposition, hormonal status, infection, and pharmacological agents. Additionally, cellular studies of psoriasis have shown that epidermal cells demonstrate increased rates of cell turnover approximately 7 to 8 times that of normal skin cells with increased cellular proliferation through reduction in G1 arrest. In combination with radiation therapy, these cellular changes may increase risks of the Koebner phenomenon.
Reports of radiation-induced Koebner phenomenon were historically seen in patients with psoriasis treated with low-energy photons through Grenz-Ray or superficial x-ray therapy. Only a few clinical cases have reported the Koebner phenomenon in patients with neoplasm treated with high-energy photon (in the MV range) radiation therapy. In breast cancer, the Koebner phenomenon has been reported in patients who received standard WBRT for breast conserving therapy (50 Gy at 2 Gy per fraction), postmastectomy radiation therapy to the chest wall (46 Gy at 2.3 Gy per fraction), and palliative radiation (30 Gy at 3 Gy per fraction). Very little is known regarding the relationship between dose per fraction and the Koebner phenomenon. In a recent prospective study by Ben-Yosef et al, 6 patients with cancer with psoriatic lesions present within the targeted irradiation field were recruited. They received radiation therapy with daily single-fraction dose ranging from 1.8 to 2.0 Gy. Neither flare-up of existing psoriatic lesions nor the Koebner phenomenon in surrounding normal-appearing skin was observed in any of the patients at up to 6 months of follow-up, leading to the postulation that daily radiation doses ≤2.0 Gy per fraction is tolerable in patients with psoriasis.

In the setting of breast-conserving therapy, radiation plays an important role in treatment. Traditionally, WBRT in early-stage breast cancer patients is delivered with conventional fractionation of 2 Gy per fraction for a total of 50 Gy. The goal of fractionating radiation treatment is to avoid late tissue toxicity; this is important because breast-conserving treatment emphasizes cosmetic outcomes. There is growing evidence suggesting that breast tumors behave more similarly to late-responding normal tissue, with a low α/β ratio as opposed to rapidly dividing tumors. This supports the usage of a hypofractionated radiation course in treating breast cancer patients. Hypofractionated WBRT with 42.56 Gy in approximately 3 weeks is both hypofractionated and accelerated compared with standard fractionated radiation therapy. This contributes to increased risks for both late and acute toxicities, respectively. In the case of our patient, the possible risk factors for maximum Koebner phenomenon include receiving both higher dose per fraction and an accelerated treatment course. This may increase acute phase tissue reactions given the increased cellular turnover rate of epidermal cells from psoriasis. In additional, her contralateral breast irradiation may have increased her systemic inflammatory response. In patients with a medical history of psoriasis requiring breast conserving irradiation, standard fractionation WBRT may be a better option than hypofractionated irradiation.

References

1. Weiss G, Shemer A, Trau H. The Koebner phenomenon: Review of the literature. *J Eur Acad Dermatol Venereol*. 2002;16:241-248.
2. Pedace FJ, Muller SA, Winkelmann RK. The biology of psoriasis. An experimental study of the Koebner phenomenon. *Acta Derm Venereol*. 1969;49:390-400.
3. Bizzozero E. *Sur le Phénomène de Koebner Dans le Psoriasis, Psoriasis Factice par le Prof. Enzo Bizzozero*. Masson; 1932.
4. Sagi L, Trau H. The Koebner phenomenon. *Clin Dermatol*. 2011;29:231-236.
5. Camargo CM, Brotas AM, Ramos-e-Silva M, Carneiro S. Isomorphic phenomenon of Koebner: Facts and controversies. *Clin Dermatol*. 2013;31:741-749.
6. Schreiber GJ, Muller-Runkel R. Exacerbation of psoriasis after megavoltage irradiation. The Koebner phenomenon. *Cancer*. 1991;67:588-589.
7. Lindelof B. Grenz-Ray therapy. *Hautarzt*. 1989;40:4-7.
8. Champion RH, Rook A, Wilkinson DS, Ebling FJG, Rook A. *Rook/Wilkinson/Ebling Textbook of Dermatology*. 6th ed. Malden, MA: Blackwell Science; 1998.
9. Charalambous H, Bloomfield D. Psoriasis and radiotherapy: Exacerbation of psoriasis following radiotherapy for carcinoma of the breast (the Koebner phenomenon). *Clin Oncol*. 2000;12:192-193.
10. Isohashi F, Konishi K, Umegaki N, Tani T, Koizumi M, Yoshioka Y. A case of bullous pemphigoid exacerbated by irradiation after breast conservative radiotherapy. *Jpn J Clin Oncol*. 2011;41:811-813.
11. Tomlinson MJ. Psoriasis and radiotherapy. *Clin Oncol*. 2001;13:145.
12. Ben-Yosef R, Soyfer V, Vexler A. Radiation therapy in cancer patients with psoriasis. The fractionated daily dose and the Koebner phenomenon. *Radiother Oncol*. 2005;74:21-23.
13. Ray KJ, Sibson NR, Kiltie AE. Treatment of breast and prostate cancer by hypofractionated radiotherapy: Potential risks and benefits. *Clin Oncol*. 2015;27:420-426.