A rare adverse skin reaction after 8 Gy of radiation therapy to the thoracic spine: case report and review of the literature

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ABSTRACT

A 60-year-old woman with breast cancer metastatic to the bones experienced no adverse skin reaction at the lumbar spine after a single 8-Gy photon-beam fraction prescribed to a depth of 5 cm. However, a subsequent treatment to the thoracic spine using the same dose, fractionation, and technique resulted in skin erythema and permanent hyperpigmentation. After careful investigation, no differences were identified in her concurrent use of possibly radiosensitizing medications during the various radiotherapy treatments nor in possible errors of treatment planning and radiation delivery. To our knowledge, this is the first case report to document that, with similar medications, a previous skin response to a given radiotherapy dose, fraction, and technique may not be predictive of subsequent skin response to similar radiotherapy.

KEY WORDS

Acute side effects, bone metastases, hyperpigmentation, palliative radiation, radiation dermatitis

1. CASE DESCRIPTION

A 60-year-old woman was treated with a left lumpectomy and axillary dissection for premenopausal receptor-negative, node-negative left breast carcinoma in 1996. This surgery was followed by adjuvant local radiotherapy of 50 Gy in 25 fractions to the whole breast, with no adjuvant systemic therapy. No unusually severe skin toxicity was reported or observed by the patient at that time or on subsequent follow-up visits.

In 2002, this woman was diagnosed with a solitary biopsy-proven, estrogen and progesterone receptor–positive, human epidermal growth factor receptor 2 (HER2/*neu*)–negative bone metastasis at the fourth lumbar vertebra (L4). Her postmenopausal status being confirmed, she was treated with letrozole and monthly pamidronate. In December 2006, when her disease progressed on treatment, letrozole was discontinued, tamoxifen was started, and pamidronate was continued. In January 2007, a single 8-Gy fraction of radiation was prescribed to L3–L5 for pain control. At that time, the patient's spinal alignment was noted to be normal, with no lumbar lordosis or thoracic kyphosis. Radiation was delivered using a Siemens Mevatron linear accelerator (Siemens Canada, Mississauga, ON), with the patient in a prone position. A single posterior 6-MV photon beam, prescribed to a depth of 5 cm, was delivered using a field size of 9.0×9.0 cm. At 6 weeks post treatment, the patient reported no pain or adverse skin erythema (grade 0).

In March 2007, progression of the patient's bone disease became evident, and she was treated with exemestane, while continuing on pamidronate. In May 2009, the patient presented with a 5-week history of localized pain at the T11 vertebra that a stepwise increase of analgesic management was not controlling. She was therefore treated with a single 8-Gy fraction of radiation to the painful T10–T12 vertebrae for pain relief. Radiation was delivered using an Elekta Synergy Beam Modulator (Elekta, Stockholm, Sweden), with the patient in a supine position on a foam mattress atop a Medical Intelligence iBEAM Evo couchtop (Elekta). A single posterior 6-MV photon beam, prescribed to a depth of 7 cm, was administered using a field size of 8.8×8.0 cm.

In August, the patient returned for more radiotherapy for a painful right iliac spine, and at that time, she mentioned experiencing an unexpected burning sensation at the irradiated site during the thoracic spine treatment. Furthermore, she noticed grade 3 erythema on her back immediately after treatment that eventually resulted in permanent hyperpigmentation. She did not apply any additional creams at that time (Figure 1).

The present case study highlights the possibility of localized skin erythema and permanent hyperpigmentation from a conventional radiation dose of 8 Gy to the spine in a patient with no history of adverse reactions from previous radiotherapy.

2. DISCUSSION

The normal tissue tolerance dose at 5% within 5 years after radiotherapy ($TD_{5/5}$) is documented [1] to be 50 Gy in 25 fractions for 100 cm^2, 60 Gy in 30 fractions for 30 cm^2, and 70 Gy in 40 fractions (including a boost dose to the tumour bed) for 10 cm^2. Localized acute skin toxicity from exposure to external-beam radiation nearing these doses for cancer treatment includes any combination of erythema and dry and moist desquamation. Side effects correlate with the total dose delivered, the fraction size and schedule, and individual patient differences [2]. Depending on severity, these side effects may limit the clinically acceptable radiation dose delivered to the patient. Furthermore, acute skin toxicity may result in permanent hyperpigmentation, which can be debilitating to the patient. When radiation is delivered over the course of 4–7 weeks, this side effect is often anticipated. However, because this particular patient received approximately 8 Gy in 1 fraction to a 16.8-cm^2 skin surface, and because that dose was well below the skin tolerance for radiation, the consequent erythema and hyperpigmentation were quite unexpected. Moreover, to our knowledge, this is the first report to document that the absence of skin toxicity from an earlier, similar treatment is not necessarily predictive of how the same patient's skin may respond to future radiation treatments for bone metastases.

We investigated the two main possibilities for this unusual skin reaction. The first is related to possible radiation sensitization from concurrent medications, and the second, to treatment planning and delivery of radiotherapy.

2.1 Radiosensitizers As a Cause of Acute Skin Erythema and Permanent Hyperpigmentation

Hyperpigmentation either during radiotherapy treatment or as a radiation recall phenomenon has previously been documented in the literature as a result of concurrent chemotherapy drugs or other radiosensitizing agents [2,3]. Anecdotally, we have noticed that patients who experience skin erythema from one radiotherapy treatment tend to experience similar side effects from future treatments. Table I lists the prescription and non-prescription medications, herbal products, and topical agents used by the patient since 2007 while on radiotherapy treatment.

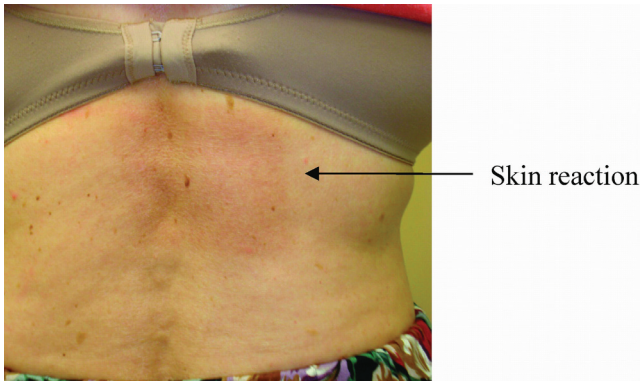

FIGURE 1 *Hyperpigmentation 3 months post radiation treatment (8 Gy in 1 fraction).*

2.1.1 Phototoxicity from Amitriptyline

Phototoxicity from amitriptyline, an antidepressant, has been reported in only 1 case in the literature, in which a 45-year-old woman experienced a 1-month history of hyperpigmentation in irradiated skin [4]. In the present case, the patient was on this medication consistently during her radiotherapy treatments (Table I); however, no hyperpigmentation manifested from either the lumbar or the iliac spine treatment. It

TABLE I All prescription and non-prescription medications, herbals, and topic agents used by the patient concurrently with each course of radiotherapy from 2007 to 2009

Site irradiated	*Date*	*Agents used*
Lumbar spine (L4)	January 2007	Amitriptyline
		Pamidronate
		Tamoxifen
		Peppermint tea occasionally
		NOT USED: lotion, sunscreen, or tanning lotion on skin
Thoracic spine (T11)	May 2009	Amitriptyline
		Exemestane
		Lorazepam as needed
		Acyclovir ointment to lips for cold sore
		NOT USED: vitamins, minerals, herbals, complementary medicine; lotion, sunscreen, or tanning lotion on skin; soap or shampoo different from that used during previous radiation to spine; chemotherapy
Iliac spine	August 2009	Amitriptyline
		Exemestane
		Lorazepam as needed
		Acetaminophen as needed
		Vitamin D occasionally
		NOT USED: soap or shampoo different from that used during previous radiation to spine; chemotherapy

therefore seems unlikely that amitriptyline was the cause of her thoracic spine skin reaction.

2.1.2 Radiation Recall from Tamoxifen

Patients that have already undergone radiotherapy treatment are known to sometimes experience radiation recall at a later date. This phenomenon occurs when patients receive chemotherapy months or years after the radiation treatment and an inflammatory reaction manifests as skin erythema localized to the previously irradiated skin. The exact mechanism for this cascade of events is still poorly understood [2,3]. Although cases of radiation recall have been reported for patients on tamoxifen treatment [2,3], the timing of this toxicity does not correlate with the experience of our patient. She was taking tamoxifen when she received radiotherapy in 2007 and experienced no acute or late skin erythema. Tamoxifen was discontinued before the subsequent radiotherapy treatments, when she observed the skin erythema that left permanent hyperpigmentation at the thoracic spine. Subsequently, no acute toxicity was observed for the same dose of radiation to the iliac spine 3 months later. Because tamoxifen use preceded the radiation treatment of interest, our patient's condition does not fit the definition of radiation recall, and tamoxifen is unlikely to be a causative agent for the adverse skin reaction.

2.1.3 The Aromatase Inhibitor Exemestane

Our patient was not on exemestane when she received radiotherapy treatment in 2007; however, she was taking this drug during her radiation treatment in 2009. Exemestane is a steroidal aromatase inhibitor that irreversibly binds to and inactivates aromatase. It inhibits the peripheral conversion of androgens to estrogens, leading to a greater than 90% reduction in circulating estrogen levels, and it produces estrogen suppression of a magnitude similar to that with the nonsteroidal aromatase inhibitors [5]. Given that estrogen is known to protect the skin, suppression of estrogen may have stimulated the skin reaction. However, observation of a skin reaction and permanent hyperpigmentation in only 1 of 2 treated areas (thoracic, but not iliac spine) with the same total dose, fraction, and treatment schedule is unusual. The literature contains no case reports of exemestane-induced skin toxicity with radiation. Moreover, we anecdotally observe many patients who routinely receive 50 Gy of breast radiotherapy concurrently with exemestane treatment and do not experience unusual skin toxicity. Therefore, although exemestane cannot completely be ruled out as a radiosensitizer, the evidence suggests that this possibility is unlikely [5].

2.1.4 Other Medications

A literature search uncovered no adverse events related to radiation in combination with pamidronate, lorazepam, vitamin D, or acetaminophen [6].

2.2 Radiation Planning and Delivery

The treatment that produced our patient's reaction was a single 8-Gy fraction of radiation, prescribed at a depth of 5 cm and delivered using 6-MV photons and a single direct posterior beam. The field size of 8.8×8 cm was produced using a multileaf collimator and encompassed 1 vertebral body above and below the affected T11 vertebra. The patient was in the supine position on a foam mattress, and the source-to-surface distance was 100 cm at the middle of the foam mattress. This radiation plan and set-up is standard within our department for the treatment of bone metastases. A thorough review of all technical parameters, including the monitor units of radiation delivered, beam energy, radiation output, and beam stability in the radiation plan and treatment record did not reveal any errors (Figure 2).

Often, palliative patients who are treated for bone metastases are planned and treated in the supine position on a foam mattress. This approach alleviates pain and discomfort during the 20–30 minutes that the patient remains still on the treatment table for treatment set-up and delivery. However, from a dosimetric perspective, this approach is not ideal—mainly because of the loss of a skin-sparing effect from the presence in the path of the beam of the linear accelerator's couch top and mattress, and from the inability of the radiation therapist to clinically visualize the light-field on the patient. This loss of skin-sparing effect may have contributed to our patient's skin reaction. A dose distribution accounting for the treatment couch and mattress estimated the skin dose at 95% of the prescribed dose. However, the variability between the dose indicated by the planning system and the dose at the patient's actual skin surface is unknown and would have to be clinically measured. A possible recommendation would be to consider testing the actual variability of the dose

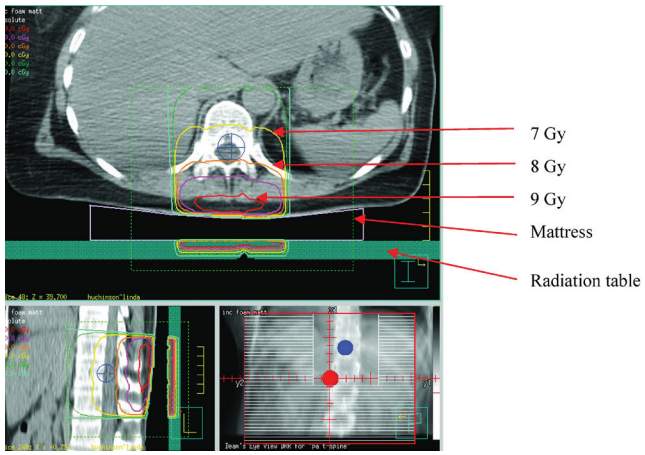

FIGURE 2 Dosimetry of the thoracic spine field (using the radiation planning system), showing that the prescribed dose of 8 Gy was received.

realized on a patient's skin from this dose, fractionation, and technique before moving to consider other options for treatment delivery.

The difference in the observed skin reactions may be related to differences in the electron contamination of the photon beams used to treat the lumbar and thoracic spine. For the lumbar spine, the set-up was prone, with no obstructions between the gantry head and the patient's skin; electron contamination would therefore result from the linear accelerator itself. We measured the surface dose in a phantom to be 14% of the maximum dose, approximating 1.4 Gy on the patient's skin. However, for the thoracic spine, the patient was supine for the treatment, and the couch top and foam mattress were in the beam's path; the surface dose in that case was measured directly using thermoluminescent dosimeters. The dosimeters were placed in the centre of the field on top of the foam mattress and underneath a thick Solid Water (Gammex rmi, Middleton, WI, U.S.A.) phantom. The skin dose was estimated to be 8.14 Gy. That dose is higher than the dose with the lumbar spine treatment, but most patients at our centre are positioned and treated in this manner, and the dose is within normal tissue tolerance and does not usually manifest as a skin reaction after a single 8-Gy treatment [1].

3. CONCLUSIONS

We report a patient who experienced a rare adverse skin reaction to a conventional radiotherapy treatment of 8 Gy in 1 fraction to the thoracic spine, using a standard supine patient set-up. Because the radiation dose delivered was well below the $TD_{5/5}$ for skin, the radiation planning technique was conventional, and the patient had experienced no adverse skin reactions from earlier radiotherapy treatments, this side effect was unexpected. All medications concurrent with the treatments delivered since 2007 were examined for possible radiosensitizing effects, and none explained the patient's acute erythema and permanent hyperpigmentation specific to the thoracic spine. The patient's radiotherapy planning and delivery were also carefully reviewed for error, and it was determined that all aspects accorded with the treatment prescribed by the physician. No case reports in the literature suggest the predictive nature of skin reactions or the absence of skin toxicity for previously prescribed radiotherapy treatment when medication history is accounted for. We still do not know the reason for this unusual skin reaction.

4. REFERENCES

1. Emami B, Lyman J, Brown A, *et al.* Tolerance of normal tissue to therapeutic radiation. *Int J Radiat Oncol Biol Phys* 1991;21:109–22.
2. Singer EA, Warren RD, Pennanen MF, Collins BT, Hayes DF. Tamoxifen-induced radiation recall dermatitis. *Breast J* 2004;10:170–1.
3. Kundranda MN, Daw HA. Tamoxifen-induced radiation recall dermatitis. *Am J Clin Oncol* 2006;29:637–8.
4. Sandra A, Srinivas CR, Deshpande SC. Photopatch test reaction to amitriptyline. *Contact Dermatitis* 1998;39:208–9.
5. Paridaens R, Dirix L, Lohrisch C, *et al.* Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. *Ann Oncol* 2003;14:1391–8.
6. Lamberg M, Rotem C, Fenig E, Koren R, Ravid A. Vitamin D protects keratinocytes from deleterious effects of ionizing radiation. *Br J Dermatol* 2009;160:151–61.

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