

## Teaching Case

# The Potentiation of Radiosensitization by Concomitant Treatment With Radiation Therapy and a PDL-1 Inhibitor in Cutaneous Squamous Cell Carcinoma



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Received February 18, 2022; accepted June 29, 2022

## Introduction

Skin cancer, the most common form of cancer worldwide, continues to increase in incidence annually.<sup>1</sup> Skin cancer can be divided into 2 groups: melanoma and non-melanoma. Of the nonmelanoma cancers, the basal cell subtype is the most common, followed by cutaneous squamous cell carcinoma (cSCC).<sup>2</sup>

Cutaneous SCC is typically risk stratified into risk categories based on its propensity for recurrence. High-risk cSCC lesions are typically treated with Mohs micrographic surgery or excisions with complete circumferential peripheral and deep margin assessment. When excision yields positive margins, resection to clear the margins or radiation therapy (RT) is considered.<sup>3</sup> Radiation therapy is the mechanism of inducing double-stranded DNA damage and thereby perpetuating tumor cell death with underlying cytotoxic mechanisms.<sup>4</sup> A common adverse effect of radiation therapy includes radiation dermatitis (RD), described as cutaneous changes,

typically within 90 days of treatment. Patients can expect to see a resolution of RD within 2 to 4 months after the last treatment.<sup>5</sup> The National Cancer Institute categorizes radiation dermatitis in severity scales (grades 1-5).<sup>6</sup>

The most common treatment modality for melanoma is surgical resection if localized; otherwise, targeted therapy with immune check point inhibitors (ICIs) can be considered. PD1/PDL-1 and CTLA-4 are ICIs currently recommended for treatment of malignant melanoma.<sup>7</sup> A range of adverse effects of immunotherapy can be noted during or after treatment; 1 potential manifestation is immunotherapy dermatitis.<sup>8</sup> This refers to a cutaneous immune-related adverse event within 6 weeks of the initial ICI dose.<sup>9</sup> A generalized, maculopapular rash is observed in patients receiving anti-PDL1/PDL-1 therapy. Depending on reaction severity, successful treatment includes topical and/or oral corticosteroids along with discontinuation of the immunotherapy.<sup>10</sup> Dermatitis is associated with improved outcomes of cancer treatment compared with patients who do not develop such adverse reactions.<sup>11</sup>

The combination of ICIs and RT has been examined in the clinical trial setting.<sup>12</sup> There are ongoing clinical trials that have been designed to evaluate the safety and efficacy of combining RT with ICI.<sup>12</sup> Here, we present a case of a male patient with a diagnosis of metastatic melanoma followed by a metachronous diagnosis of cSCC, who

Sources of support: This work had no specific funding.

Disclosures: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data sharing statement: All data generated and analyzed during this study are included in this published article and its supplementary information files.

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<https://doi.org/10.1016/j.adro.2022.101021>

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required curative-intent RT for cSCC while receiving maintenance immunotherapy for melanoma.

## Case Report

An 86-year-old male patient with a medical history of atrial fibrillation, coronary artery disease, hypertension, and hypercholesterolemia presented to a dermatologist in September 2017 for a punch biopsy of a lesion on the scalp. Results of the biopsy showed cutaneous melanoma. Further testing with a bone scan and a computed tomography (CT) scan of the chest revealed multiple lung nodules and osseous lesions suggestive of pulmonary and osseous metastases. The patient was subsequently referred to hematology and oncology for treatment of metastatic malignant melanoma. Before treatment, magnetic resonance and CT imaging of the brain were also conducted, showing vasogenic edema in the left frontoparietal areas without obvious mass. Given the clinical evidence of metastatic disease at diagnosis, the patient was started on intravenous pembrolizumab, 200 mg, every 3 weeks in October 2017.

After 2 months of therapy, chest CT showed a 32% decrease in the target pulmonary lesions. Repeat imaging after 3 months showed continued improvement on both brain and chest CT. The physical examination was notable for nearly complete resolution of the scalp lesion, with residual hyperpigmented microfoci. In May 2018, the patient presented to the dermatologist with lesions suspicious of SCC on the right cheek; however, the patient declined biopsy at that time. Thereafter, he was noted to have a cystic 1.5- to 2-cm mass in the left posterior scalp with a few scaly lesions over both cheeks. Fine-needle aspiration of the cystic lesion on the posterior left scalp was negative for cancer in June 2018.

The patient was subsequently lost to follow-up with dermatology. He returned to the dermatologist's office in April 2020. Biopsies were taken from lesions on the left superior and malar cheek and the left central mandibular cheek. These lesions showed squamous cell carcinoma, well and moderately differentiated. The patient was referred to radiation oncology in May 2020. External beam radiation was recommended for the left facial cheek cancers and forehead skin cancer. Skin brachytherapy was recommended for nasal tip cancer. Owing to the multifocal skin disease involving the patient's left cheek, a larger treatment field was necessary to encompass the multiple lesions with adequate clinical margin (Fig. 1). To encompass the 2 biopsy-proven left forehead lesions with an adequate clinical margin, a treatment area, depicted in Fig. 1, was selected. The patient underwent CT simulation for radiation therapy treatment planning with a 0.5-cm thickness superflab bolus placed on the patient's left cheek and left forehead. Using a Varian TrueBeam linear accelerator and Eclipse treatment planning software, the radiation dose was calculated with Monte Carlo calculations and heterogeneity corrections. The treatment area of the left cheek and left forehead was prescribed 55 Gy in 20 daily fractions with 6 MeV electrons. This dose prescription was consistent with National Comprehensive Cancer Network (NCCN) guidelines for curative-intent treatment of cSCC.

Radiation to the left cheek was done from mid-June to mid-July for a period of 4 weeks. During the last week of his external beam RT treatment course, the patient developed a disproportionate amount of RD in the left cheek and forehead region, which quickly progressed in severity. The patient's RD was best characterized as significant desquamation and ulceration leading to bleeding with minimal trauma (Fig. 2). Management included daily topical Silvadene Cream in addition to twice-daily wound



**Fig. 1** Preradiation planning. The identification and markings of location for radiation therapy before beginning therapy are shown.



**Fig. 2** Postradiation evaluation. The patient's reaction immediately after completing radiation therapy is shown, with significant radiation dermatitis noted.

dressing changes. The severe RD slowly regressed. Gradually, during a course of 3 months, the RD had significant improvement but not complete resolution. Pembrolizumab was continued during this course. The patient successfully underwent brachytherapy, 8.0 Gy in 5 fractions every other day prescribed to a 5-mm depth, for the left nasal tip cancer without significant adverse effects. Upon close follow-up, all the treated cutaneous malignancies showed no evidence of recurrence after treatment. A short while later, the patient died from unrelated causes.

## Discussion

To our knowledge, this is the first case report that highlights the unexpected adverse effect of high-grade RD when combining RT and ICI. Typically, the grade and volume of anticipated RD are directly proportionate to the prescribed RT dose, fractionation, and RT treatment area. This patient received 55 Gy in 20 daily fractions, over 4 weeks, for the treatment of SCC.<sup>3</sup> This dose and fractionation are consistent with NCCN guidelines. Although development of either grade 1 or grade 2 RD after RT is most known, our patient developed grade 3 dermatitis within the treatment region.

The classification of acute RD is based on the Common Terminology Criteria for Adverse Events; this inflammatory reaction occurs upon exposure to biologically effective levels of ionizing radiation.<sup>6</sup> Our patient developed grade 3 dermatitis, characterized by moist desquamation in areas other than the skin folds and creases, with associated bleeding induced by trauma or abrasions. Toxic effects after radiation therapy result from a combination of the dose, schedule, or volume of organ treated.<sup>6</sup> Our patient received a hypofractionated radiation therapy

prescription, consistent with NCCN guidelines.<sup>3</sup> The volume of skin subjected to radiation included his left superior forehead and the left central malar and mandibular cheek. These areas characterize an overall limited volume of skin surface.

For our patient, in the setting of his RT dose, frequency, and volume, the development of the grade 3 RD was out of proportion to the treatment. The patient had continued to receive pembrolizumab every 3 weeks while he received RT. He had been undergoing treatment with pembrolizumab for metastatic melanoma for approximately 3 years before his cSCC diagnosis. Thus, immunotherapy dermatitis could not be the diagnosis, because the time span exceeded the expected presentation within 6 weeks of initial immunotherapy dose. This prompted the concern for radiosensitization as the key underlying difference in our patient's presentation. The synergistic effect of radiation therapy and ICIs is currently being investigated in preclinical and clinical trials; however, in this clinical case, with 2 separate cutaneous malignancies, concomitant treatment for both was warranted.<sup>12</sup>

This case prompted inquiry into the underlying pathophysiology of the presentation. Radiation therapy induces tumor cell death, prompting the immunologic activation of antigen-presenting cells and thereby increasing antigen presentation to T cells. Through a stepwise progression, the inflammatory cytokines and immune cells yield anti-tumor and anti-self-responses. This concept is pivotal for patients on immunotherapy, because their immune system is heightened and thus induces further inflammatory effects.<sup>13</sup> Additionally, tumor cell recognition is augmented after radiation, leading to immune system activation.<sup>14</sup> Studies have suggested the ability of radiation therapy to heighten immunogenicity of tumors and thus increase the effect of simultaneous immunotherapy.<sup>15</sup>

After evaluation of similar case reports, we found a report by Sibaud et al, in which the authors noted acute skin reactions taking place after receiving pembrolizumab, which was administered just 3 days after RT for the treatment of metastatic melanoma. In this case, RT was directed to the knee and elbow. Thereafter, the patient was started on pembrolizumab, at which point the patient developed an acute skin reaction on the elbow but not the knee. This was defined as a radiosensitization reaction, a reaction occurring within a window of 7 days between radiation and immunotherapy.<sup>16</sup>

## Conclusion

Ultimately, our case is unique because the patient had a preceding diagnosis of metastatic melanoma requiring treatment with immunotherapy and subsequently developed another skin cancer requiring treatment with RT. Currently, there are multiple clinical trials under way that evaluate the safety and efficacy of concomitant use of ICI with RT. In the absence of prospective evidence, this case report serves as a source of knowledge for clinicians who might find themselves in a clinical situation that merits concomitant use of RT and ICI. Given the increasing prevalence of cSCC and the increasing use of ICI for various malignancies, we anticipate clinicians encountering this scenario more commonly.

## References

1. Patrinely JR Jr, Dewan AK, DB Johnson. The role of anti-PD-1/PD-L1 in the treatment of skin cancer. *BioDrugs*. 2020;34:495–503.
2. Corchado-Cobos R, García-Sancha N, González-Sarmiento R, Pérez-Losada J, Cañueto J. Cutaneous squamous cell carcinoma: From biology to therapy. *Int J Mol Sci*. 2020;21:2956.
3. National Comprehensive Cancer Network. Squamous cell skin cancer (version 2.2021). Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/squamous.pdf](https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf). Accessed July 10, 2021.
4. Liu Y, Dong Y, Kong L, Shi F, Zhu H, Yu J. Abscopal effect of radiotherapy combined with immune checkpoint inhibitors. *J Hematol Oncol*. 2018;11:104.
5. Leventhal J, Young MR. Radiation dermatitis: Recognition, prevention, and management. *Oncology (Williston Park)*. 2017;31:885–899.
6. Bray FN, Simmons BJ, Wolfson AH, Nouri K. Acute and chronic cutaneous reactions to ionizing radiation therapy. *Dermatol Ther (Heidelb)*. 2016;6:185–206.
7. Davis LE, Shalin SC, Tackett AJ. Current state of melanoma diagnosis and treatment. *Cancer Biol Ther*. 2019;20:1366–1379.
8. Kwok G, Yau TC, Chiu JW, Tse E, Kwong YL. Pembrolizumab (Keytruda). *Hum Vaccin Immunother*. 2016;12:2777–2789.
9. Geisler AN, Phillips GS, Barrios DM, et al. Immune checkpoint inhibitor-related dermatologic adverse events. *J Am Acad Dermatol*. 2020;83:1255–1268.
10. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2015;26:2375–2391.
11. Chhabra N, Kennedy J. A review of cancer immunotherapy toxicity: Immune checkpoint inhibitors. *J Med Toxicol*. 2021;17:411–424.
12. Chicas-Sett R, Morales-Orue I, Rodriguez-Abreu D, Lara-Jimenez P. Combining radiotherapy and ipilimumab induces clinically relevant radiation-induced abscopal effects in metastatic melanoma patients: A systematic review. *Clin Transl Radiat Oncol*. 2017;9:5–11.
13. Hwang SJ, Carlos G, Wakade D, et al. Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: A single-institution cohort. *J Am Acad Dermatol*. 2016;74:455-461.e1.
14. El Chediak A, Shamseddine A, Bodgi L, Obeid JP, Geara F, Zeidan YH. Optimizing tumor immune response through combination of radiation and immunotherapy. *Med Oncol*. 2017;34:165.
15. Ngwa W, Irabor OC, Schoenfeld JD, Hesser J, Demaria S, Formenti SC. Using immunotherapy to boost the abscopal effect. *Nat Rev Cancer*. 2018;18:313–322.
16. Sibaud V, David I, Lamant L, et al. Acute skin reaction suggestive of pembrolizumab-induced radiosensitization. *Melanoma Res*. 2015;25:555–558.