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PII: S2452-1094(22)00127-0
DOI: https://doi.org/10.1016/j.adro.2022.101021
Reference: ADRO 101021

To appear in: *Advances in Radiation Oncology*

Received date: 18 February 2022
Accepted date: 29 June 2022

Please cite this article as: C.A. Fadel , S.U. Danak , J. Jhaveri , M.D. Caudell , The potentiation of radio sensitization by concomitant treatment with radiation therapy and a PDL-1 inhibitor in cutaneous squamous cell carcinoma, *Advances in Radiation Oncology* (2022), doi: https://doi.org/10.1016/j.adro.2022.101021

The potentiation of radio sensitization by concomitant treatment with radiation therapy and a PDL-1 inhibitor in cutaneous squamous cell carcinoma

Radio Sensitization in Cutaneous Carcinoma

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Data Sharing Statement: All data generated and analyzed during this study are included in this published article (and its supplementary information files).

Funding: None.

Conflict of Interest Statement: The authors listed above certify that they have no affiliations or involvement in any organization with any financial interest or non-financial interest in the subject discussed in this manuscript.

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Abstract

The incidence of nonmelanoma skin cancer (NMSC) and cutaneous melanoma (CM) is rising, and it is common to have synchronous or metachronous diagnosis of both malignancies in one patient. NMSC is often treated with surgery or radiotherapy (RT), and CM with surgery followed by immune check point inhibition (ICI) or ICI alone. Radiation dermatitis is a side effect of RT, while immunotherapy dermatitis can occur with ICIs. Reports of concurrent RT and ICI for two underlying malignancies are scarce. To guide concurrent or sequential treatment, we report a case of an 86-year-old male with a metachronous diagnosis of CM and cutaneous squamous cell carcinoma (cSCC), undergoing RT for cSCC while on maintenance ICI for melanoma. Punch biopsy of a scalp lesion revealed melanoma, with evidence of distant metastases. Pembrolizumab was started and maintained. Two years later, histopathology of a left cheek lesion revealed cSCC. He received curative intent RT for cSCC but developed consequential grade III dermatitis. The RT dermatitis was disproportionately higher for the given dose, which we suspect was from concurrent use of ICI and RT. This is the first known report of radiation sensitization with pembrolizumab for malignant melanoma, followed by RT for cSCC. Due to the increasing utilization of ICI for cutaneous malignancies, concurrent RT usage merits further investigation. We recommend careful consideration when using curative intent RT with concurrent ICI. This report supports evaluation of interactions of ICI and RT in prospective randomized clinical trials, some of which are already underway.

Introduction:

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

cSCC is typically risk stratified into risk categories based on its propensity for recurrence. High risk cSCC lesions are typically treated with Mohs micrographic surgery (MMS) or excisions with complete circumferential peripheral and deep margin assessment (CCPDMA). When excision yields positive margins, re-resection to clear the margins or radiotherapy (RT) is considered [3]. Radiation therapy is the mechanism of inducing double stranded DNA damage and thereby perpetuating tumor cell death with underlying cytotoxic mechanisms [4]. A common side 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 following the last treatment [5]. The National Cancer Institute categorizes the radiation dermatitis in severity scales (Grade 1 to 5) [6].

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

The combination of ICIs and RT has been examined in the clinical trial setting [12]. There are ongoing clinical trials that have been designed to evaluate the safety and efficacy of combining RT with ICI [12]. Here, we present a case of a male patient with a diagnosis of metastatic melanoma followed by a metachronous diagnosis of cSCC, who required curative intent RT for cSCC while receiving maintenance immunotherapy for melanoma.

Case Report:

An 86-year-old male patient with past medical history of atrial fibrillation, coronary artery disease, hypertension, and hypercholesterolemia first presented to the dermatologist in September 2017 for a punch biopsy of a lesion on the scalp. Results of the biopsy showed cutaneous melanoma. Further testing with bone scan and 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. Prior to treatment, magnetic resonance imaging (MRI) brain and CT 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 two months of therapy, CT chest showed a 32% decrease in the target pulmonary lesions. Repeat imaging again after 3 months showed continued improvement on both CT brain and CT Chest. Physical exam was notable for near complete resolution of the scalp lesion, with residual hyperpigmented microfoci. In May 2018, the patient presented to the dermatologist with lesions suspicious of squamous cell cancer (SCC) on the right cheek, however, the patient declined biopsy at that time. Thereafter, he was noted to have a cystic 1.5-2 cm mass in the left posterior scalp with a few scaly lesions over both cheeks. Fine-needle aspiration was negative for cancer in June 2018 of the cystic lesion on the posterior left scalp.

Patient was subsequently lost to follow-up with dermatology. He returned to the dermatologist office in April 2020. Biopsy was taken from lesions on the left superior and malar cheek, along with left

central mandibular cheek. These lesions showed squamous cell carcinoma, well and moderately differentiated. 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. Due 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 (Figure 1). To encompass the two biopsy-proven left forehead lesions with an adequate clinical margin, a treatment area depicted in Figure 1 was selected. Patient underwent CT Simulation for radiotherapy treatment planning with 0.5 cm thickness superflab bolus placed on the patient's left cheek and left forehead. Using Varian Truebeam linear accelerator and Eclipse treatment planning software, 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 guidelines (NCCN) for curative intent treatment of cSCC.

Radiation to the left cheek was done from mid-June to mid-July, over a total four-week period. 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. Patient's RD is best characterized as significant desquamation and ulceration leading to bleeding with minimal trauma (Figure 2). Management included daily topical Silvadene cream in addition to twice daily wound dressing changes. The severe RD slowly regressed. Gradually, over the course of 3 months, the RD had significant improvement, yet not complete resolution. Pembrolizumab was continued during this course. He successfully underwent brachytherapy, 8.0 Gy in 5 fractions every other day prescribed to 5 mm depth, for the left nasal tip cancer without significant side effects. Upon close follow-up, all the treated cutaneous malignancies showed no evidence of recurrence after treatment. A short while later, the patient passed away from unrelated causes.

Discussion:

To the best of our knowledge, this is the first case report that highlights the unexpected side effect of high-grade RD when combining RT and ICI. Typically, the grade and volume of anticipated RD is directly proportionate to the prescribed RT dose, fractionation, and RT treatment area. The patient above received 55 Gy in 20 daily fractions, over 4 weeks, for the treatment of SCC [3]. This dose and fractionation are consistent with NCCN guidelines. While it is most known to develop either grade one or grade two RD after RT, 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 (CTCAE); this inflammatory reaction occurs upon exposure to biologically effective levels of ionizing radiation [6]. 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. Toxicity from radiation therapy is a combination of dose, schedule, or volume of organ treated [6]. Our patient received hypo-fractionated radiotherapy prescription, consistent with NCCN guidelines [3]. 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 three weeks while he received RT. The patient had been undergoing treatment with Pembrolizumab for metastatic melanoma for approximately three years, prior to his cSCC diagnosis. Thus, immunotherapy dermatitis cannot be the diagnosis, as the time span exceeds 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 radiotherapy and ICIs is currently being investigated in pre-clinical and clinical trials, however, in this clinical case, with two separate cutaneous malignancies, concomitant treatment for both was warranted [12].

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 antitumor and anti-self-responses. This concept is pivotal for patients on immunotherapy, as their immune system is heightened, and thus inducing further inflammatory effects [13]. Additionally, tumor cell recognition is augmented post-radiation, leading to immune system activation [14] Studies have suggested the ability of radiotherapy to heighten immunogenicity of tumors, and thus increase the effect of simultaneous immunotherapy [15].

After evaluation of similar case reports, we found a report by Sibaud et. al., where the authors noted acute skin reactions taking place after receiving pembrolizumab, which was administered just three 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 they developed an acute skin reaction only on the elbow, but not the knee. This was defined as a radiosensitization reaction, a reaction occurring within a window of seven days between radiation and immunotherapy [16].

Conclusion:

Ultimately, our case is unique because the patient had a preceding diagnosis of metastatic melanoma requiring treatment with immunotherapy, and subsequently developing 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 + ICI. Given the increasing prevalence of cSCC and increasing use of ICI for various malignancies, we anticipate clinicians encountering this scenario more commonly.

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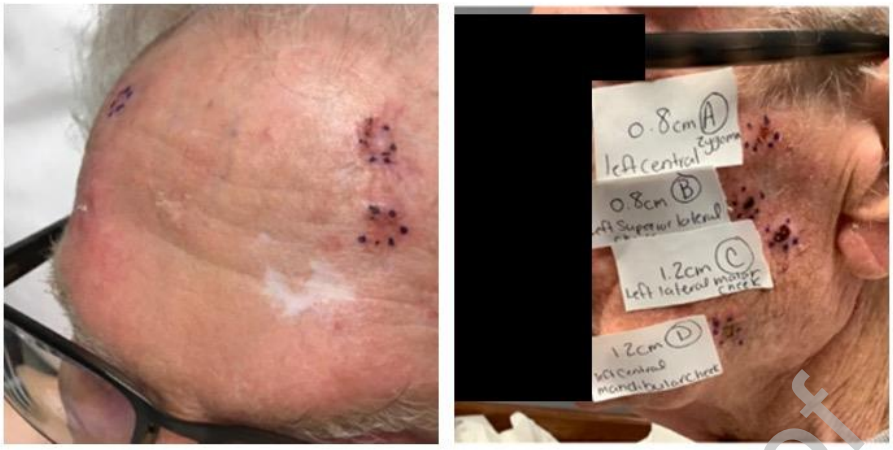
Figure Legends:

Figure 1: Pre-radiation planning: This demonstrates the dentification and markings of location for RT prior to beginning therapy.

Figure 2: Post-radiation evaluation: This demonstrates the patient's reaction immediately after completing radiotherapy, with significant RD noted.



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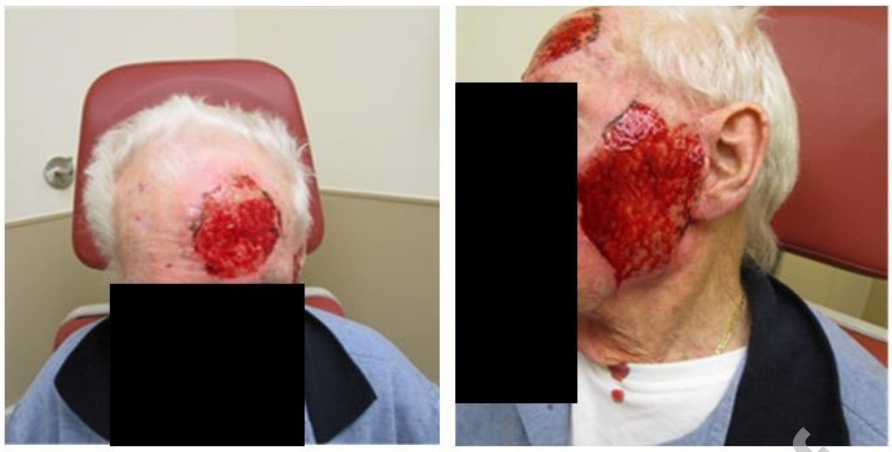

Figure 2: Post-radiation evaluation: This demonstrates the patient's reaction immediately after completing radiotherapy, with significant RD noted.

Declaration of interests

☒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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: