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Case Report

Sorafenib induced radiation recall dermatitis after spine radiosurgery

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Radiation recall dermatitis has been documented to occur in previously irradiated skin (within the radiation port) the administration of some chemotherapeutic agents. Clinically, it can occur weeks or months after radiation therapy, and resembles the appearance of acute radiation skin reaction. The patterns of the reaction correspond with radiation fields and skin doses. We report a case of recall dermatitis 8 weeks after of spine radiosurgery initiated by the use of a multi-targeted tyrosine kinase inhibitor, Sorafenib, used for treatment of hepatocellular carcinoma.

INTRODUCTION

Radiation recall dermatitis (RRD) is skin reaction, which resembles acute radiation dermatitis in appearance and occurs in previously irradiated skin weeks to months post radiation treatment after the administration of a new medication [1-3]. Although radiation recall dermatitis is well known with multiple reported cases, the underlying mechanism is still not well understood. During this "recall" phenomenon, healthy-appearing previously irradiated skin becomes erythematous and edematous with desquamtation and in rare cases necrosis [1-3]. The patterns of the reaction correspond with radiation fields and skin doses [4-6]. The trigger for this reaction is the initiation of a new medication after radiation, historically cytotoxic chemotherapeutic agents [1-3]. More recently other agents included targeted molecular therapies have also been implicated [6-12]. Sorafenib is a multi-targeted tyrosine kinase inhibitor used in the treatment of advanced liver and kidney cancers [13-15]. We describe the development of radiation recall dermatitis induced by sorafenib in a patient previously treated with spine radiosurgery.

CASE REPORT

A 55-year-old male presented with a four month history of back pain. As part of his initial workup for back pain, he had a spine MRI. This showed an osseous lesion in the L2 vertebral body with a soft tissue mass involving the psoas muscle. A subsequent body CT scan showed multiple ill-defined hypodense lesions in the liver. He also had an elevated AFP of 1895 ng/ml. The patient had a CT-guided biopsy of the L2 mass, and the pathology revealed metastatic hepatocellular carcinoma. Due to patient's intractable back pain, he was treated with spine radiosurgery with a single radiation dose of 20 Gy to the L2 vertebral body including the paraspinal mass. The treatment consisted of seven intensity-modulated radiosurgical beams from the posterior direction conforming to the target. He tolerated the radiosurgery procedure well, and he had no complications or skin reactions after the radiosurgery.

Six weeks after spine radiosurgery, the patient started systemic treatment with sorafenib 400 mg twice a day orally. After two weeks of sorafenib therapy (8 weeks after radiosurgery), the patient complained of he dry, itchy, flaky skin and redness on his lower back On physical exam he was found to have several patchy erythematous band-like lesions in the same axial plane across his lower back with dry desquamation consistent with grade 2 skin reaction according to the NCI common toxicity criteria, which was not apparent at routine

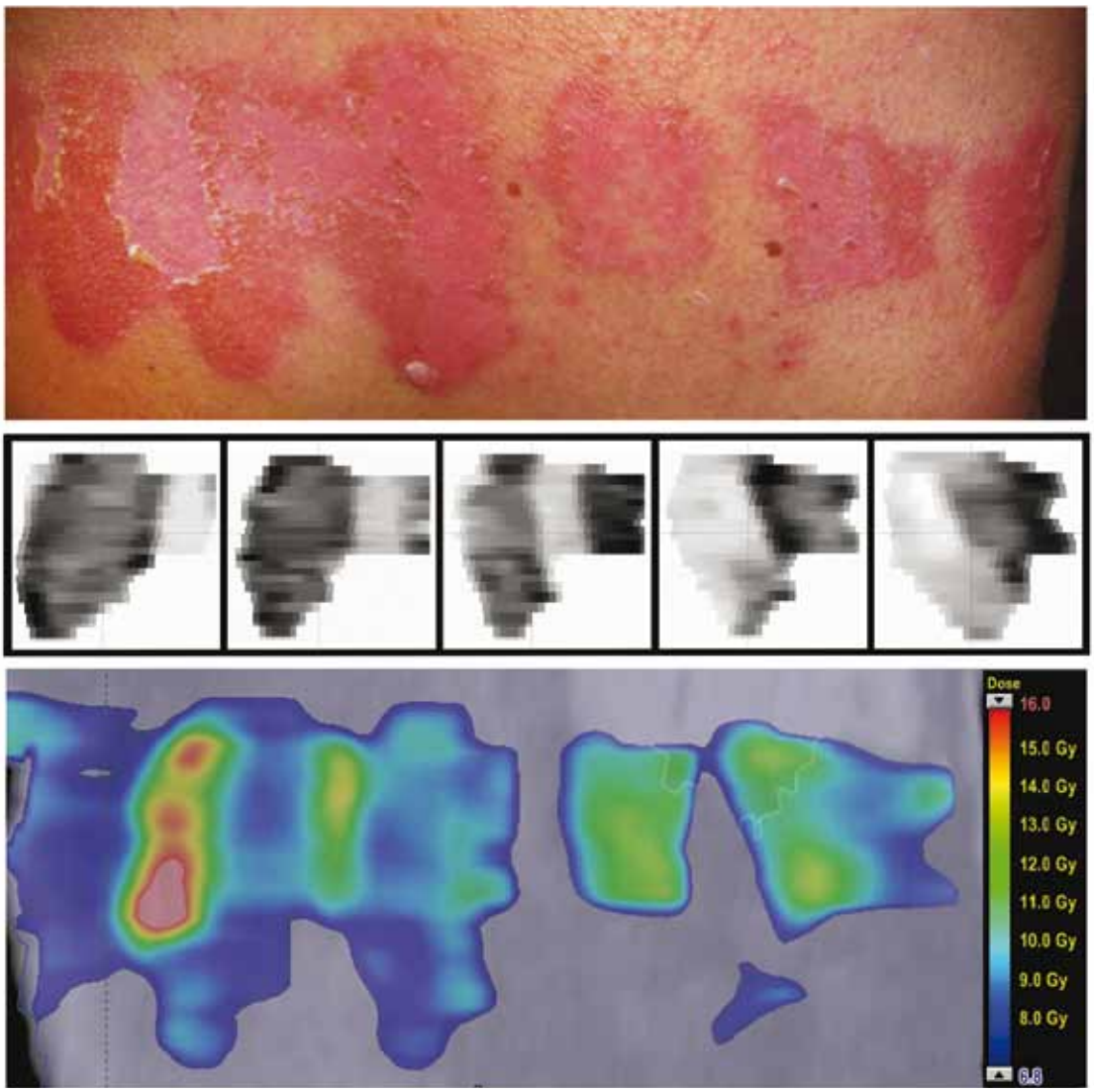

Figure 1. Top Panel: *Appearance of grade 2 skin dermatitis eight weeks after the patient underwent spine radiosurgery to the L2 vertebral body and two weeks after starting sorafenib chemotherapy. Areas of erythema and dry desquamation correspond with radiation skin dose and intensity.* ***Middle Panel:*** *Fluence maps showing the radiation dose intensity in each beam with darker color representing greater fluence and beam intensity. Areas of highest fluence correspond with the geographic shape, distribution, and severity of skin reaction and areas of low fluence show no reaction.* ***Bottom Panel:*** *Surface skin dose in treated area with dose wash. Colors represent doses as noted on right side of image. Surface skin dose around 7 Gy corresponds well to areas of erythema, while areas receiving >10 Gy correlate with areas of dry desquamation.*

follow-up the week prior. These were located in separate geographic areas corresponding to the radiation ports from radiosurgery (Fig. 1). He received no medical therapy for his dermatitis and the lesions resolved over the next two weeks.

DISCUSSION

To determine if the patient's delayed skin reaction was related to his radiation treatment, the radiation plan was reviewed and compared to the geographic skin lesions on the patient's back. Review included detailed analysis of beam orientation, radiation fluence maps, estimation on skin surface dose and the isodose lines showing radiation doses to tissue and skin (Fig.1 middle and bottom panel). The radiation fluence maps and skin dose correlated to the geographic shape and distribution of skin lesions. The severity of desquamation appears to correspond to the patterns of intensity-modulated radiation beams and the skin dose. Skin dose of seven Gy appeared to be a threshold for erythema, while areas receiving more than ten Gy

had dry desquamation in addition to erythema. No skin reaction was seen in areas with dose less than seven Gy. These findings suggest a threshold as well as a possible radiation dose relationship necessary for the development and severity of RRD. We believe that this patient's skin reaction was a recall phenomenon induced by sorafenib, because in our experience of single dose spine radiosurgery, there were no acute or long-term skin complications after spine radiosurgery [16]. Acute radiation skin reactions usually develop within four weeks of completing radiation therapy and a maximum of six weeks [17]. However, this patient's dermatitis occurred about eight weeks after radiation and two weeks after starting sorafenib. The time sequence from the initiation of oral therapy to the development of dermatitis compares well with previously described cases of radiation recall dermatitis [1-2].

Radiation recall dermatitis was first described by D'Angio *et al* in 1959, when they described a "latent" radiation effect producing erythema and desquamation in previously irradiated skin shortly after actinomyocin D therapy was initiated [3]. Since that time many cases of radiation recall dermatitis have been described mainly after the administration of cytotoxic agents, but cases after initiating therapy with antiestrogens, cholesterol-lowering agents, and antibiotics have been reported [1-3,7-9]. More recently targeted cancer agents including monoclonal antibodies and small molecules have been implicated in this phenomenon [6,10-12].

Sorafenib is a relatively new oral agent used in advanced solid tumor including advanced renal cell carcinoma and hepatocelluar carcinoma [13-15]. It is a potent small molecule inhibitor of multiple tyrosine kinases including Vascular epithelial growth factor receptor 2, Platelet derived growth factor receptor, and fibroblast growth factor-1 and elements of the Ras/Raf/MEK pathway [13-14]. It is generally well tolerated and is often associated with cutaneous effects like hand-foot skin reaction, squamoproliferative lesions, rash, desquamation, alopecia, erythema and dry skin [14,18].

Several hypotheses have been generated to explain this phenomenon including vascular damage, epithelial stem cell depletion, epithelial stem cell sensitivity, and drug hypersensitivity reaction [2]. In the presented case one possible explanation for mechanism is the inhibition of tyrosine kinases, specifically VEGFR2. After a large single fraction of radiation there is a loss of basal cells followed by period of exponential reepithelialization and then a rapid increase in the density of endothelial cells [19]. Correspondingly after radiation treatments, VEGFR2 positive vascular progenitor cells increase in circulation and can remain elevated for weeks after treatment [19]. These cells are likely important for normal repair, re-epithelization, and repopulation of endothelial cells after radiation injury. It may be possible that inhibition of VEGF receptor 2 or other tyrosine kinases in these cells and in the treated area by sorafenib could impair these processes leading to erythema and desquamation in irradiated fields.

Although the exact etiology and mechanism of RRD is unknown and poorly understood, several studies have suggested a relationship between skin radiation dose and radiation recall dermatitis. Total accumulated skin doses in excess of 18-20 Gy with fractionated radiation treatments were necessary to elicit recall dermatitis [4-6]. We speculate that the recall skin reaction in our case also has a radiation dose relationship. Our data suggests a skin threshold doses for single fraction doses of about 7 Gy for erythema and 10 Gy for desquamation. This was shown by comparison of skin image with skin doses from the planning system. Skin in the radiation ports in areas with high fluence had more severe desquamation and skin reaction, while adjacent low fluence areas in the same radiation port manifested milder or even no reaction.

To the best of our knowledge, this is the first report of sorafenib induced radiation recall dermatitis after a radiosurgical procedure. This case illustrates that with newer radiation techniques (radiosurgery, intensity-modulated radiation therapy, stereotactic body irradiation) patterns of acute skin reaction and radiation recall dermatitis may present in an unusual manner due to radiation beams oriented in multiple directions and with varying intensities. This case illustrates the possibility of unexpected reaction from the combination of new biologically targeted therapy and modern radiation technology.

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