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Case Report

Radiation and Immunotherapy Extended Life in a Patient Who Failed Chemotherapy and Immunotherapy Trials: Implications of Radiation Abscopal Effect

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Abstract

Stage IV bladder cancer has been previously noted to have poor survival outcomes. The current standard of care is focused on systemic therapy with radiation only being utilized for the management of painful osseous metastases and controlling other symptoms. Our report introduces a patient with multiple, large mediastinal metastases who failed multiple rounds of systemic therapy, including immune therapy, who responded to radiation therapy twice, and had a complete response to immune therapy accompanying the second round of partial-volume low-dose radiation therapy. The patient, who was initially considered for hospice, is currently alive one year after the second course of radiation followed by immunotherapy and 2 years after the first course of palliative radiation.

Introduction

Patients with stage IV bladder cancer are noted to have poor survival outcomes, only 16% of patients are alive 5 years after diagnosis [1]. Radiation is traditionally only utilized for pain management of osseous metastases and controlling urinary symptoms in metastatic bladder cancer [2], however radiation has been seen to be effective in treating mediastinal metastases in esophageal cancer patients [3]. In this case, we will introduce a patient with massive mediastinal metastases who failed multiple rounds of systemic therapy, including immunotherapy trials. This case is interesting as he experienced a dramatic response to radiation therapy twice, and because following the second course of radiation, which was low dose, partial volume, the patient experienced a complete response to Nivolumab therapy.

Case Description

This is a 67 year old male diagnosed with high grade transitional cell carcinoma of the bladder, staged as pT4N0M0 in May 2010. The patient was first treated with gemcitabine and cisplatin, followed by total cystectomy. Adjuvant therapy involved cisplatin and gemcitabine with concurrent radiation. After treatment, there was no evidence of disease. In September 2011, a mediastinal metastasis was confirmed as having

bladder origin. The patient was treated with Pemetrexed, followed by Taxol with Cetuximab, and then gemcitabine in September 2013. In October 2013, the patient presented for a Jak 2 inhibitor clinical trial. In April 2014, the patient was treated on an IDO inhibitor clinical trial. The tumor continued to progress, and weight loss due to progressive dysphagia was observed (Figure 1).

Figure 1a: CT Response After Palliative Radiation

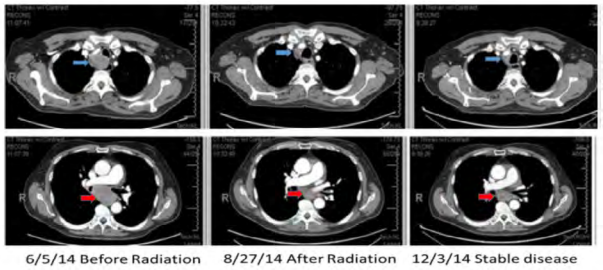


Figure 1b: Change of Tumor Size Throughout Treatment

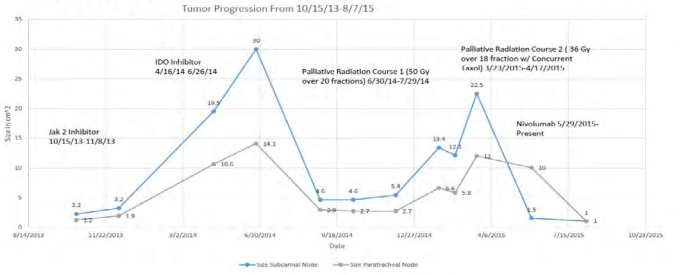


Figure 1c:Changes in Weight Over Time

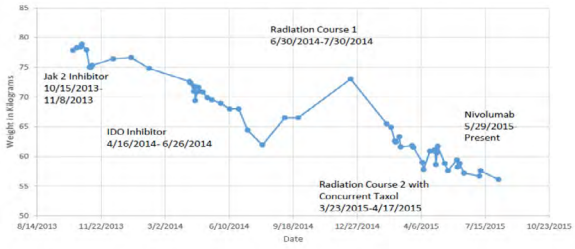
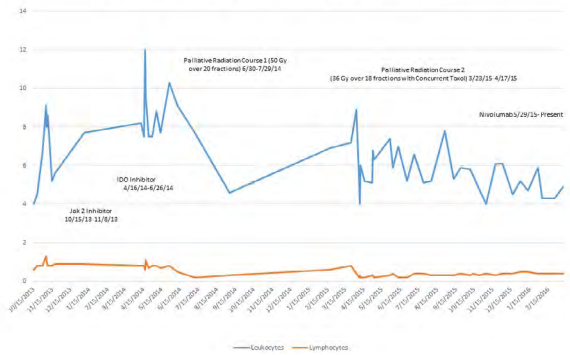


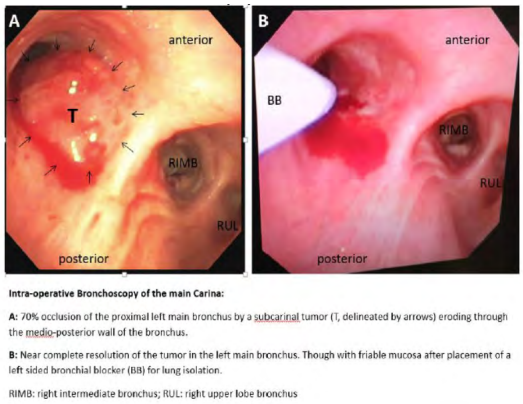
Figure 1d: Immune Cell Levels Throughout Treatment



Figures 1 (a,b,c,d). Tumor progression, regression, weight loss, and immune cells.

This figure shows changes of tumor size on computed tomography (CT) images (1a and 1b) and changes of weight (1c) before radiation, after radiation, and stable disease 4 months after the final radiation treatment. The upper image displays the subcarinal node, while the lower image displays the paratracheal node. A dramatic response to treatment is seen in both nodes, as the subcarinal node was reduced from 30 cm^2 to 4.6 cm^2. The paratracheal node shrank from 14.1 cm^2 to 2.9 cm^2 after the 1st course of radiation. The tumors are seen to increase in size under Jak 2 and IDO inhibitor therapies, and experience a dramatic response to treatment during the first course of radiation therapy. Then, the tumors grew in size until the second course of radiation when they again saw a dramatic decrease in tumor size. Figure 1c displays the patient's weight over the course of tumor progression and treatment. Note the weight loss (16 kg over 2 years), along with the weight gain (11 kg over 4 months) during and after the first course of radiation therapy. Figure 1d shows the patient's immune cells throughout treatment.

A gastric tube was placed for nutrition. He was considering hospice or a course of palliative radiation therapy. He was treated with a dose of 50 Gy in 20 fractions to all visible tumors from 6/30/14 to 7/29/14, using 6MV photons and intensity modulated radiation therapy technique (IMRT). He tolerated the treatment well, with improvement of dysphagia. As shown on Figure-1, the subcarinal node decreased in volume by 88%, and the paratracheal node decreased by 86% (Figure-1). After treatment, the patient no longer needed his gastric tube, and was able to eat and function normally until spring 2015. A chest CT on March 16th, 2015 revealed tumor progression (Figure 1). A bronchoscopy on March 26th, 2015 revealed a 70-80% obstruction of the left main bronchus (Figure 2).



Intra-operative Bronchoscopy of the main Carina:

A: 70% occlusion of the proximal left main bronchus by a subcarinal tumor (T, delineated by arrows) eroding through the medio-posterior wall of the bronchus.

B: Near complete resolution of the tumor in the left main bronchus. Though with friable mucosa after placement of a left sided bronchial blocker (BB) for lung isolation.

RIMB: right intermediate bronchus; RUL: right upper lobe bronchus

Figure 2. Endobronchial tumor response after second line of radiation therapy (36 Gray concurrent with Taxol).

This figure shows the left main bronchus, imaged endobronchially, before and after the second line of radiation therapy (36 Gray [Gy] with Taxol).

Due to extensiveness of the disease, he was not considered to

be a candidate for surgical resection. His mediastinal lesion was negative for PD-L1 expression, thus not eligible for an active trial. There were no treatment options available at that time. The case was discussed in tumor board, and the patient was given a month to live and recommended to enter hospice. Palliative radiation was discussed with the patient as a very high risk option. The patient was consented for serious complications including treated-related death. A dose of 32 Gy radiation was delivered to the obstructive subcarinal tumor, using MRT technique, from 3/23/2015-4/17/2015. Low dose of Taxol was given concurrently for radiation sensitization. The patient tolerated the treatment without any notable side effects. The obstruction of the left main bronchus was 10% in May 2015 (Figure 2). PET scan showed a great response to treatment with little residual tumor with minimum FDG activity of radiated subcarinal tumor. The FDG avid upper mediastinal mass (not re-irradiated) was slightly smaller in size. His overall performance improved; the patient started Nivolumab at end of May, 2015. PET scan on August 7, 2015 showed almost complete response with minimal residual disease. The non-radiated upper mediastinal tumors also had almost complete response (Figure 3).

The second course of radiation, low dose to part of progressed tumors, relieved the bronchial obstruction. This stabilized the disease outside of radiation field and almost complete response to Nivolumab (anti-PD-L1 treatment) may contribute to radiation abscopal effect, similar to that reported in melanoma [4]. It is interesting to note that PD-L1 inhibitors without radiation often have limited response. In a study of 30 bladder cancer patients positive for the PD-L1 receptor, 47% (N=14) experienced an objective response, while 26% (N=8) of patients experienced stable disease and 25.6% (N=8) experienced progressive disease, but only 7% (2 patients) were seen to have a complete response [5]. The lack of PD-L1 expression in this patient's tumor, along with the complete response was also very interesting. In melanoma clinical trials with Nivolumab, the response rate was 17% in PD-L1 negative patients, compared with 44% in PD-L1 positive patients, however in the PD-L1 negative patients that do respond, the radiographic response is often dramatic (75-100% reduction in tumor burden), very similar to that of our case. The fact our patient experienced a complete response to the Nivolumab (especially with the tumor's PD-L1 negative status), may have been impacted by the abscopal effect.

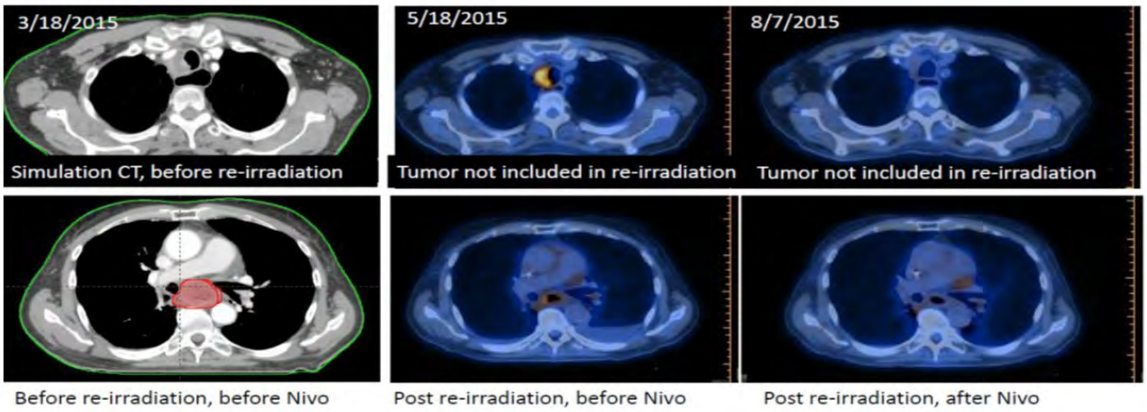


Figure 3. Potential radiation abscopal effect.

This figure shows remarkable response of subcarinal tumor after 36 Gy re-irradiation, and stable disease of upper mediastinum tumor. After re-irradiation to the subcarinal tumor, the non-irradiated upper mediastinal tumor also showed a modest response. Most interestingly, the upper mediastinum tumors also achieved complete response to immunotherapy. The patient is currently on his **15th cycle** of Nivolumab, and is alive and well without evidence of tumor progression at **12 months** after the second course of radiotherapy.

Discussion

This case is unique as palliative radiation remarkably prolonged survival, low dose of re-irradiation with sensitizing dose of chemotherapy generated a great local tumor response and stabilized diseases, and after re-irradiation the patient responded to immunotherapy that he failed previously. The patient had over 6 months of tumor progression free survival after the 1st course of radiation without any systemic therapy.

In previous studies, involving both humans and murine models, a halting of distant tumor progress associated with local radiation therapy (known as the abscopal effect) has been observed [4,7-9]. A murine model study found that the abscopal effect is mediated through p53 [7]. Another murine model found that in some cases when immunotherapy alone is not effective in inducing an immune effect on the tumor and neither is low dose radiation therapy to a distant target, the combination can be effective in halting distant tumor growth[8]. In a previous case report, radiation therapy was shown to increase CD4+ ICOS^{high}. This is important, because high CD4+ ICOS^{high} is associated with improved clinical benefit and overall survival in melanoma patients receiving iplimumab. Furthermore, utilization of local ablation combined with immunomodulation has also been described by electrochemotherapy with adjuvant immunogene electrotransfer [11]. A well-designed prospective study is needed to determine the potential role of radiation abscopal effect in metastatic bladder cancer.

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