Nivolumab Enhances the Inflammation of the Irradiation Field in Advanced Non–Small Cell Lung Cancer

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Introduction

Nivolumab, a fully human immunoglobulin G4 programed cell death 1 (PD-1) immune checkpoint inhibitor antibody, offers a statistically superior survival benefit over docetaxel for advanced, previously treated NSCLC.[1,2] The objective response rate of nivolumab is approximately 15%, and most of the responses have been durable and persisted after treatment discontinuation in patients who stopped therapy for reasons other than disease progression.[3,4] However, the clinical benefits of nivolumab have been limited to a subset of patients. Thus, the results of the combined use of nivolumab and radiation therapy (RT), standard chemotherapy, molecular target agents, or other immune checkpoint inhibitors are highly anticipated.[5]

The combination of RT and targeted PD-1/programmed death ligand 1 therapy synergistically activates cytotoxic T cells and reduces myeloid-derived suppressor cells, which is related to the abscopal effect in preclinical studies.[6,7] Notably, investigation of the combination of PD-1/programmed death ligand 1 inhibition and RT is also under way in clinical trials. Here, we report a patient in whom inflammation in the previous irradiation field developed after nivolumab treatment and who experienced a subsequent antitumor response not only in the irradiated field but also in lesions distant from the irradiated targeted site.

Case Report

The patient was a 73-year-old man who had previously received cytotoxic chemotherapy (carboplatin and paclitaxel) for advanced NSCLC. After six cycles of chemotherapy, a follow-up computed tomography scan revealed local recurrence of the primary lesion and progression of muscle metastasis (Fig. 1*A* and 1*B*). At that time, he had left back pain owing to muscle metastasis, and he received local RT of 40 Gy (4-Gy fractions for 10 days) for muscle metastasis. Two months after RT, nivolumab treatment was initiated (3 mg/kg every 2 weeks). There was no dermatitis, such as faint erythema or desquamation, in the irradiation field at the start of nivolumab treatment. However, after 2 weeks of treatment, dermatitis on the irradiation field suddenly developed (Fig. 2*A* and Fig. 3). Laboratory data revealed no marked leukocytosis and a C-reactive protein level (a white blood cell count of 6410/μL and C-reactive protein level of 0.19 mg/dL, respectively) showing the absence of signs of infection. The patient continued to receive nivolumab and was treated with steroid ointment for the lesion. One and a half months

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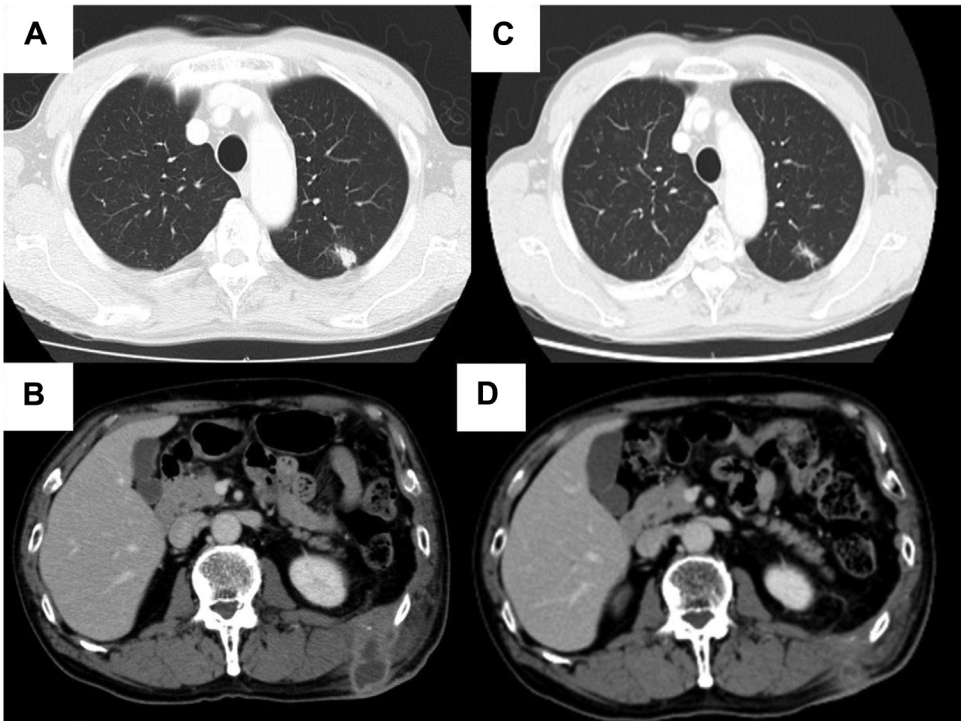

Figure 1. Computed tomography scan of muscle metastatic and primary lung lesions before (*A* and *B*) and 2 months after the initiation of nivolumab treatment (*C* and *D*).

after the initiation of nivolumab, the dermatitis distant from the tumor site improved but that around the muscle metastasis remained (Fig. 2*B*). Computed tomography demonstrated a marked improvement in muscle metastasis and the primary lesion (Fig. 1*C* and *D*). The patient was treated with nivolumab without disease progression for 4 months. Three months after nivolumab treatment, the reddish color of the skin in the previously irradiated field changed to black (Fig. 2*C*).

Discussion

The present case report demonstrates that nivolumab could enhance inflammation in the irradiation field. The lesion in the irradiated field was stable until the initial dose of nivolumab. However, dermatitis found only on

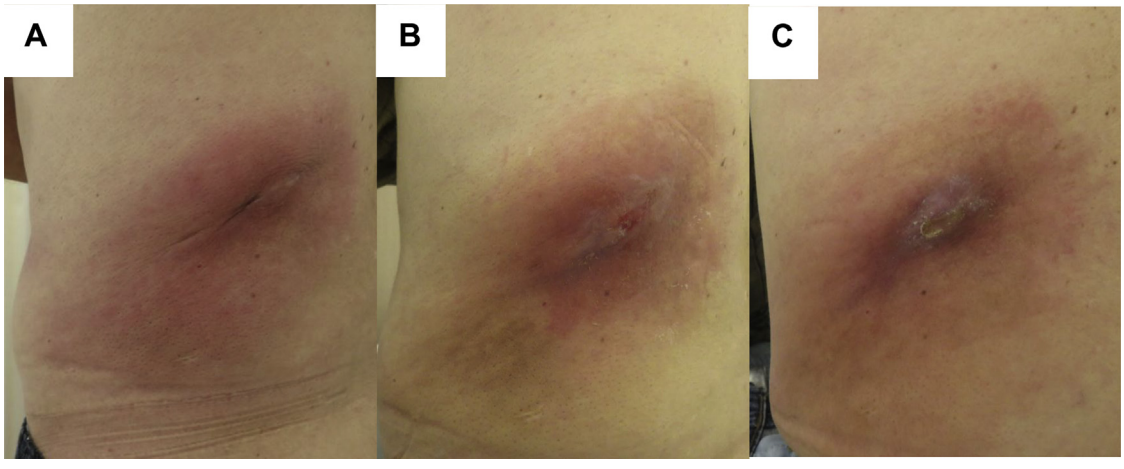

Figure 2. Dermatitis on the irradiated field at 2 weeks, 1.5 months, and 3 months after the start of nivolumab treatment (*A*, *B*, and *C*, respectively).

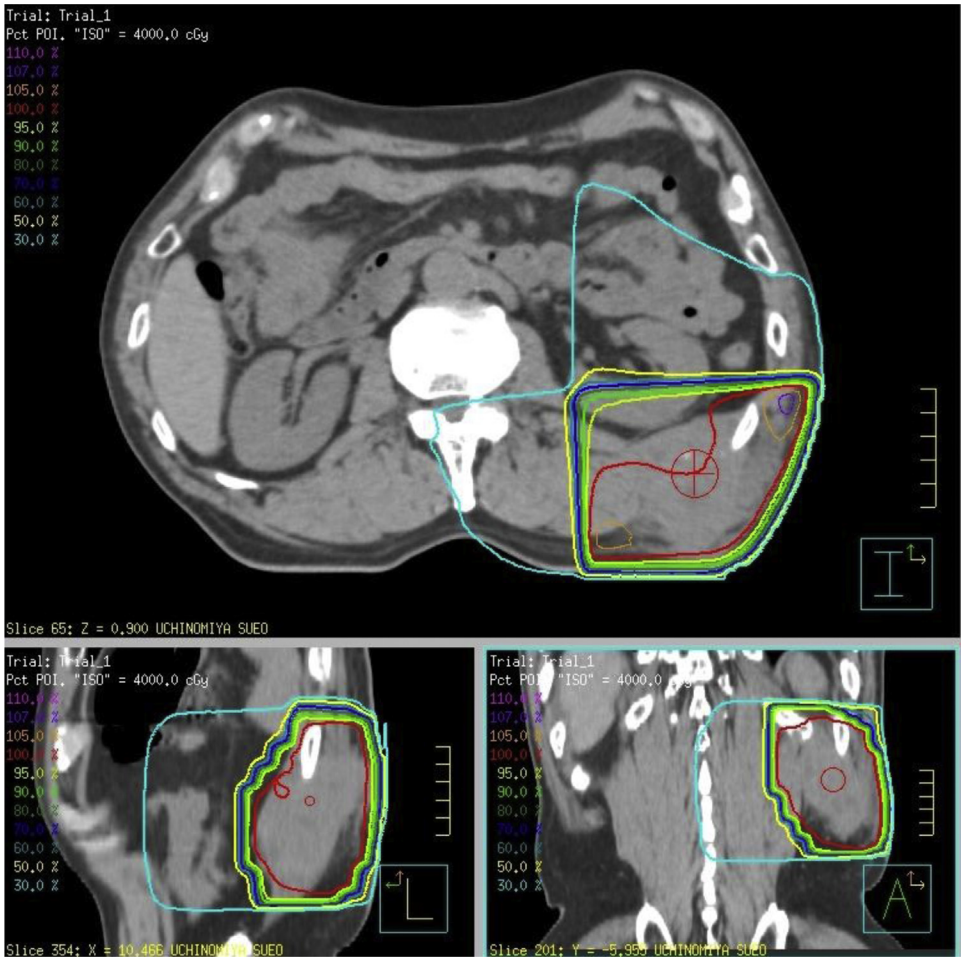

Figure 3. Dose distribution of radiotherapy to the muscle metastatic lesion.

the irradiated field developed just after the start of nivolumab treatment. In addition, the patient experienced a subsequent antitumor response not only in the irradiated field but also in lesions distant from the irradiated targeted site.

Notably, RT not only releases cancer cell antigens into the immune system but also enhances infiltration of activated T cells into the tumor microenvironment.[6] This process can induce an antitumor effect distant from the irradiation site, the abscopal effect. However, this effect is a rare phenomenon in patients receiving local RT. With the development of immune checkpoint inhibitors, such as the anti–cytotoxic T-lymphocyte antigen 4 monoclonal antibody ipilimumab and agents targeting the PD-1 pathway, the potential effect of combining these agents with RT to induce the abscopal effect has become clinically relevant. In fact, recent case reports of patients with cancer have revealed that combination therapy with local RT and immune checkpoint inhibitors induces the abscopal effect.[8,9] In addition, Shaverdian et al. recently reported that previous treatment with RT in patients with advanced NSCLC results in longer progression-free and overall survival with pembrolizumab treatment than that in patients who did not previously undergo RT.[10] In the present case, the possibility that nivolumab alone might be responsible for the response cannot be ruled out. However, this case apparently demonstrated that nivolumab treatment enhanced inflammation in the irradiation field and subsequently induced an antitumor response. Therefore, this case report supports the belief that a combination of local RT and immunotherapy, such as an anti–PD-1 agent, could be a useful strategy in improving the outcomes of immunotherapy in patients with advanced NSCLC. Further investigation of the efficacy and safety of the combination of RT and immune checkpoint inhibitors, including the timing of RT, is warranted.

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