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Case Report

Abscopal Effect after Stereotactic Body Radiotherapy with Nivolumab for Lung Metastasis of Head and Neck Cancer: A Case Report

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Keywords

Abscopal effect · Head and neck squamous cell carcinoma · Immunotherapy · Stereotactic body radiotherapy

Abstract

Introduction: The abscopal effect (AE) is a phenomenon, in which radiotherapy exerts an antitumour effect on distant lesions outside the primary irradiated area. Although immune checkpoint inhibitors have been widely studied for their potential to enhance the AE and improve patient outcomes, findings in cases of head and neck cancers remain limited. ***Case Presentation:*** We report the case of a 72-year-old man who experienced lung oligoprogression during nivolumab treatment for metastatic hypopharyngeal cancer. Stereotactic body radiotherapy (SBRT) was administered to one of the lung lesions, after which both irradiated and nonirradiated lesions regressed. Upon an 18-month follow-up period after SBRT, the patient showed no disease progression or toxicity, and continued receiving nivolumab therapy. ***Conclusion:*** The intent behind presenting this case report was to contribute to the accumulation of evidence regarding the AE in cases of head and neck cancer.

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Introduction

Radiotherapy (RT) has long been known to have an antitumour effect on distant lesions outside the primary irradiated area, a phenomenon that was described by Mole as the abscopal effect (AE) in 1953 [1]. Although the AE is rarely induced by RT alone, immune checkpoint inhibitors (ICIs) may enhance AE incidence and subsequently affect patient outcomes. Numerous studies have investigated the outcomes of combined RT and ICI treatments. Stereotactic body radiotherapy (SBRT) is often indicated as a definitive intervention in patients with oligometastasis (OM) and/or oligoprogression (OP), which involves the presence of limited distant metastases, and is also of interest as an immune-activating modality [2].

Available clinical data on AE in head and neck squamous cell carcinoma (HNSCC) are limited, and most data are available in case reports [3]. Herein, we present the case of a patient with lung OP who received nivolumab after chemoradiotherapy for hypopharyngeal cancer. SBRT was performed on one of these lesions, which resulted in AE affecting the nonirradiated lesion. Our aim was to contribute to the accumulation of evidence regarding AEs, particularly in the context of HNSCC. The CARE Checklist has been completed by the authors of this case report and is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534609).

Case Report

A 72-year-old male presented to our institution with T4aN2bM0 (stage IVA) SCC of the hypopharynx in April 2020. The expression of programmed death-ligand 1 had not been evaluated. The patient was treated at our institution with chemoradiotherapy, consisting of a total radiation dose of 70 Gy in 35 fractions using the volumetric modulated arc therapy technique with one daily irradiation 5 days a week and three cycles of high-dose cisplatin (100 mg/m^2) every 3 weeks from May to July 2020. During the treatment course, the patient developed grade 2 diarrhoea (Cancer Institute Common Toxicity Criteria for Adverse Events, version 5.0) and febrile neutropenia, in response to which he received a reduced dose of cisplatin, for a total dose of 175 mg/m^2. RT was completed without prolongation, and any acute adverse events were appropriately treated. Computed tomography (CT) imaging obtained 5 months after treatment completion revealed well-controlled neck lesions; however, several lung nodules had developed. Subsequent 18-fluoro-deoxyglucose positron emission tomography/CT showed significant accumulation in the nodules, and, therefore, he was diagnosed with multiple lung metastases (Fig. 1a). The patient received nivolumab 240 mg every 2 weeks. CT imaging findings obtained at 3 months after nivolumab initiation, showed that multiple lung metastases had almost completely regressed (data not shown); however, CT imaging obtained after 6 months of nivolumab treatment revealed the recurrence of two metastatic lesions in the upper lobe of the left lung. 18-fluoro-deoxyglucose positron emission tomography revealed significant accumulation in those two lesions, although no other metastases were detected (Fig. 1b). Based on these results, we decided to administer SBRT to the lung lesions. As the two lesions were relatively separated and it was considered unsafe to irradiate them simultaneously, we planned SBRT for the larger para mediastinal lesion first, which was to be followed by SBRT for the smaller lesion 6 months later. The patient underwent SBRT with 48 Gy in four fractions for the para mediastinal lesion (Fig. 2), and while he maintained his course of nivolumab, it was not administered the week before and after, nor during, the SBRT treatment. The patient did not experience any acute adverse events associated with the SBRT treatment, and CT imaging performed at 2 months post-SBRT revealed

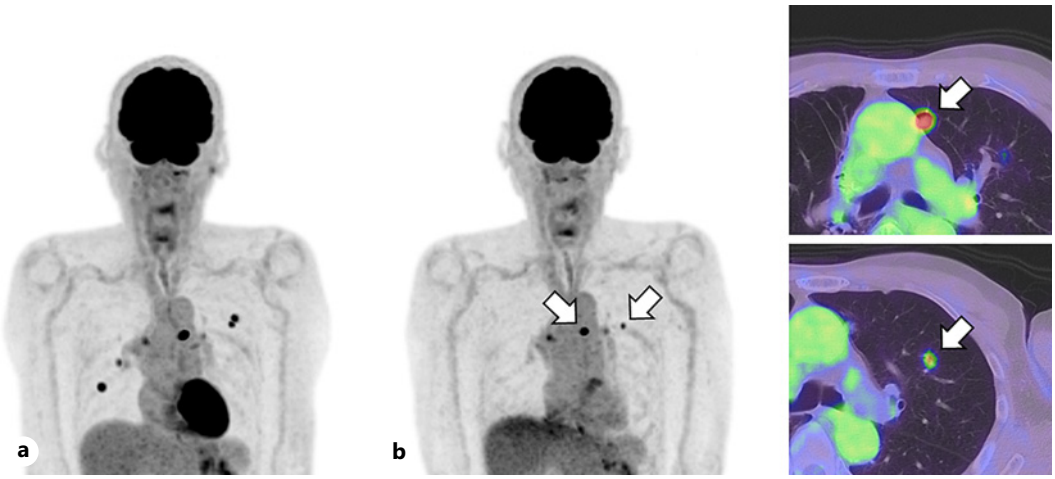

Fig. 1. 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) findings obtained 5 months after chemoradiotherapy. **a** The findings indicated that multiple metastases were observed in both lungs. **b** FDG-PET and computed tomography (CT)-fused images obtained at 6 months after nivolumab initiation indicated that multiple lung metastases completely regressed during treatment, although two recurred in the left upper lobe (arrow).

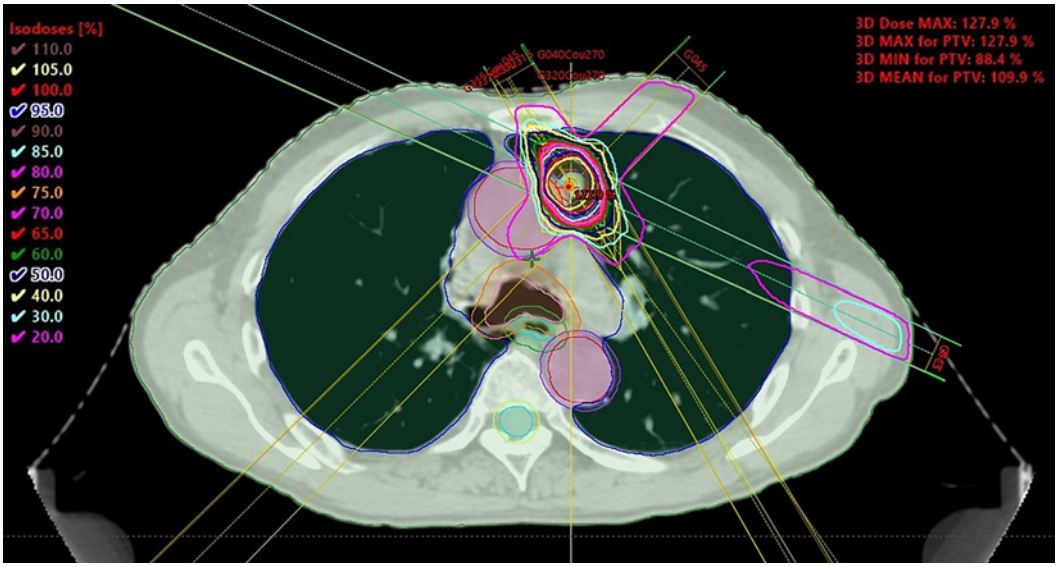

Fig. 2. Stereotactic body radiotherapy (SBRT) for the para mediastinal lesion – SBRT plans were created using noncoplanar 3D conformal fields, with 48 Gy in four fractions, 80% isodose line prescription, and 95% coverage of the planned target volume.

the regression of the irradiated lesion (Fig. 3a). Additionally, the smaller, nonirradiated lesion had also shrunk (Fig. 3b). This lesion had completely regressed at 7 months after SBRT (Fig. 3c). A follow-up examination performed at 18 months after SBRT indicated that the patient had no local or distant site progression or toxicity, and continued the nivolumab treatment. The timeline from completion of chemoradiotherapy in this patient is summarised in Figure 4.

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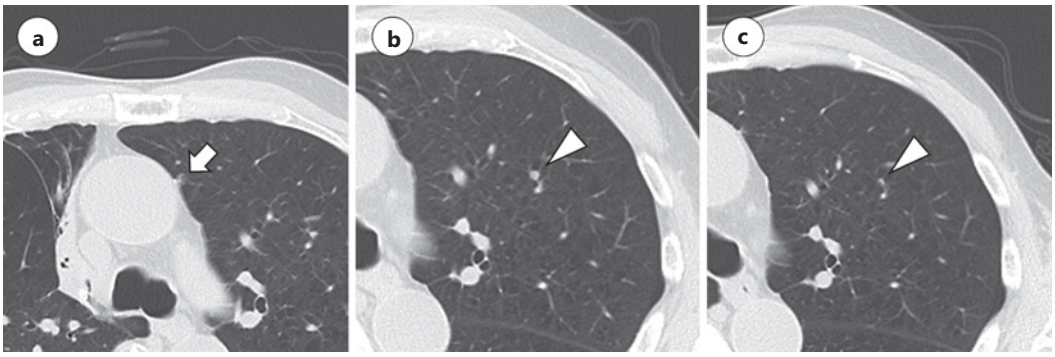

Fig. 3. CT findings at 2 and 7 months after SBRT. **a**, **b** At 2 months after SBRT, the irradiated lesion regressed (arrow), and the nonirradiated lesion shrunk (arrowhead). **c** At 7 months after SBRT, the nonirradiated lesion regressed (arrowhead).

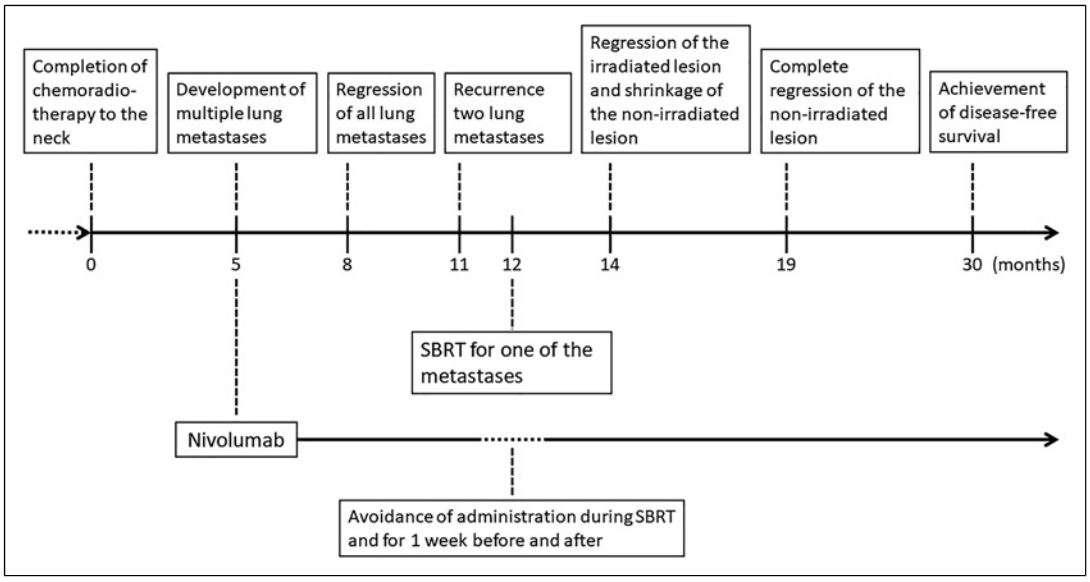

Fig. 4. A summarised timeline of the patient's course of achieving AE.

Discussion

Although the AE is currently an active area of research, the available evidence remains limited, with fewer reports specific to HNSCC, which have been primarily from case reports (Table 1) [4–7]. To our knowledge, there are no detailed reports of cases, in which SBRT for lung metastases induces the AE in patients with HNSCC.

Although RT may have an antitumour effect on lesions outside the irradiated area, this effect is rarely induced by RT alone. Historically, there have been limited reports on the AE; however, in 2012, Postow et al. reported a case of AE induced by SBRT with concurrent ipilimumab treatment in the metastatic lesions of a patient with malignant melanoma [8]. Cases of AE associated with combination SBRT/ICI therapy have become an area of active research, and various clinical trials have been conducted to examine their potential clinical significance. One such phase II trial is PEMBRO-RT [9], in which patients with at least two metastatic lesions of non-small cell lung cancer were treated with pembrolizumab, and the

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Table 1. Reports in English of the AE in patients with HNSCC

Case	Age, years/ sex	Primary lesion	Distant metastases	RT	Irradiated lesion	ICI	AE	Patient outcome
Shinde et al. [4]	75/M	Oropharynx	Lung	QUAD SHOT (14.8 Gy in 4 fractions, twice daily)	Primary and neck lymph node	Nivolumab and ipilimumab	Regression of lung metastases 2 weeks after RT	Disease-free survival for 10 months
Ellerin et al. [5]	84/F	Parotid	Lung	50 Gy in 20 fractions	Primary and neck lymph node	None	Shrinkage of lung metastases from the RT period to 6 months	Recurrence of lung metastases and death 7 months after RT
Choi et al. [6]	67/M	Lower lip	Hilar nodes, liver, and adrenal glands	SRT, 45 Gy in 5 fractions	Submandibular	Atezolizumab	Regression of all metastatic lesions	Disease-free survival for 13 months
Choi et al. [6]	69/M	Larynx	Axillary lymph nodes	SBRT, 21 Gy in 3 fractions	Axilla	Pembrolizumab	Regression of all metastatic lesions 1 month after RT	Disease-free survival for 20 months
Forner et al. [7]	57/M	Frontal and ethmoid sinuses	Lung	SRT, 30 Gy in 5 fractions	Orbit (local recurrence)	Nivolumab	Regression of lung metastases 1 month after RT	Disease-free survival for 5 months
Present case	60/M	Hypopharynx	Lung	SBRT, 48 Gy in 4 fractions	Lung	Nivolumab	Regression of nonirradiated lung lesion 7 months after RT	Disease-free survival for 18 months

RT, radiotherapy; ICI, immune checkpoint inhibitor; AE, abscopal effect; S(B)RT, stereotactic (body) radiotherapy.

outcomes were compared between those who received SBRT (24 Gy in three fractions) for one of the lesions and those who were treated with pembrolizumab alone. The results of that trial showed that although they failed to meet the criteria for the prespecified critical endpoint, the patients in the SBRT group showed a significant improvement in the overall response rate compared to those in the control group. A prospective multicenter study analysed the outcomes of SBRT for OM/OP lesions in patients undergoing ICI treatment for non-small cell lung cancer and malignant melanoma [10]. The patients in that study received SBRT (35 Gy in five fractions) only for progressive lesions. The results were good, with the AE occurring in 65% of cases. Additionally, progression-free survival was significantly better in the group which showed AEs than in the group that did not. ICIs have the potential to achieve a complete response in patients with cancer [11]. Recent studies have suggested an association between sex and ICI efficacy [12] and have examined biomarkers that predict the response to ICI therapy, such as the PD-L1 status, tumour mutational burden, and tumour-infiltrating lymphocytes [13, 14]. We believe that SBRT and AE could also be factors that increase the possibility of achieving a complete response to ICI treatment.

In the present case, SBRT with a high dose of 48 Gy in four fractions was delivered to control OM/OP. Indications for the induction for RT solely to induce the AE should be carefully determined. A randomised phase II trial of nivolumab versus nivolumab with SBRT (27 Gy in three fractions) for the treatment of metastatic HNSCC showed no improvement in patient outcomes and no evidence of AE with the addition of SBRT [15]. The authors acknowledge the insufficient sample size and the favourable results of nivolumab alone in the metastatic HNSCC control group. Similar negative results have been reported for other carcinomas [16, 17]. In these trials that aimed to induce the AE in patients with metastasis, SBRT was often delivered at relatively low doses, such as 24–30 Gy in three fractions. Therefore, clinicians should consider SBRT as a modality for the local control of OM/OP with high-dose administration rather than as a modality for immune activation with low-dose administration. Additionally, it has not been established whether SBRT and ICI should be used concurrently. In the present case, we avoided ICI administration during the SBRT period and for 1 week before and after the procedure to maintain a focus on preventing radiation pneumonia. It is possible that this concern was not valid, as a few reports have suggested that concurrent SBRT and ICI administration is safe, and there have been a few clinical trials designed to use both concurrently [18]. Recently, the predominant expert consensus was that although ICI should not be administered on the same day as SBRT, the ICI treatment cycle does not have to be omitted in favour of the SBRT schedule [19]. As it remains unclear whether the concurrent or sequential use of SBRT and ICI contributes to patient outcomes, further studies are required to clarify the effectiveness and safety of combined SBRT/ICI treatment.

In conclusion, we reported the case of a patient with HNSCC who underwent SBRT for lung OM/OP and was treated with nivolumab. The patient subsequently experienced AE, resulting in long-term disease-free survival. Clinicians should consider performing imaging evaluations based on the possibility of inducing the AE and continuing ICI treatment after controlling OM/OP with SBRT.

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Statement of Ethics

The Jichi Medical University Central Clinical Research Ethics Committee has determined that our project does not meet the "common rule" definition of human subjects' research and does not require Certified Review Board review. Written informed consent was obtained from the patient for the publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Endo M. designed this study. Takahashi S., Nagai Y., and Nishino H. were involved in the patients' management. Fukuda Y., Okada K., Ogawa K., Nakamura M., Kawahara M., and Akahane K. contributed to the data collection. Yamaguchi H., Nishino H., Mori H., and Shirai K. supervised the project. All authors approved the final manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material. Further enquiries can be directed to the corresponding author.

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Case Rep Oncol 2023;16:1345–1352
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