

The abscopal effect in head-and-neck squamous cell carcinoma treated with radiotherapy and nivolumab: a case report and literature review

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ABSTRACT

Introduction The abscopal effect is a rarely observed outcome of radiotherapy wherein there is a reduction in metastatic disease burden outside of the targeted treatment area. Likely due to an *in situ* vaccine effect of radiotherapy, the abscopal effect may be augmented by immunotherapy. This report is the first case of the abscopal effect observed in metastatic head-and-neck squamous cell carcinoma (HNSCC) treated with concurrent radiotherapy and single-agent nivolumab.

Case Description An otherwise healthy 57-year-old man underwent craniofacial resection and adjuvant chemoradiotherapy for advanced sinonasal squamous cell carcinoma. Distant metastatic disease developed shortly after primary treatment, and immunotherapy in the form of nivolumab was initiated. Subsequent oligometastatic progression despite immunotherapy prompted palliative radiotherapy to a single metastasis due to pending symptomatology. Post-radiotherapy, the abscopal effect was observed with all distant sites of metastatic disease shrinking. Five months following treatment, a sustained reduction in disease burden has been demonstrated.

Summary We present the first case of the abscopal effect in a patient with metastatic HNSCC treated with palliative radiotherapy concurrent with single-agent nivolumab immunotherapy, and only the third case of the abscopal effect in metastatic head-and-neck cancer. Dual treatment with immunotherapy and radiotherapy may be an important treatment option in the future, mediated through the abscopal effect.

Key Words Head-and -neck neoplasms, antineoplastics, radiation oncology, medical oncology

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INTRODUCTION

Head-and-neck squamous cell carcinoma (HNSCC) is the 6th most common cancer worldwide, with over 500,000 new cases diagnosed each year¹. Sinonasal cancer, constituting 5% of all head and neck malignancies, is a rare, aggressive type of head-and-neck cancer encompassing the nasal cavity and paranasal sinuses^{2,3}.

Distant metastatic disease is rare for sinonasal cancer, occurring in approximately 5% of patients⁴. Treatment options remain limited in this setting, and there

is an exceptionally high morbidity and mortality rate. Recently, immunotherapy has been used successfully in the management of treatment-resistant metastatic HNSCC, showing improved survival compared with conventional systemic therapy^{5–7}. Ongoing trials are investigating the role of first-line immunotherapy alone or in combination with chemotherapy in treatment-naïve metastatic disease⁸.

Radiotherapy is capable of generating the abscopal effect, whereby there is a reduction in tumour burden outside the targeted radiotherapy field. While occurrence of the abscopal effect is infrequent and unpredictable, the use

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of immunotherapy is believed to increase the likelihood of this occurrence⁹. There have been approximately 50 cases of abscopal effect reported in the literature, of which only 2 cases are of metastatic HNSCC^{10,11}.

This report therefore presents the 3rd such case of a reduction in distant metastatic disease burden following locoregional radiotherapy and immunotherapy in a patient with HNSCC, and the first with single-agent nivolumab. We also highlight previous cases through systematic review, as well as the proposed mechanism of the abscopal effect.

METHODS

A single-reviewer (DF) systematic literature review was carried out using MEDLINE and Google Scholar. In brief, search terms included “abscopal,” “neoplasms,” and key words descriptive of head-and-neck cancer sites, for example “oropharynx.” Google Scholar was searched with the terms “abscopal,” “head and neck,” and “carcinoma.” Searches were performed from database inception to 25 December 2019. Snowballing and reference review techniques of relevant articles were performed in order to identify additional case reports that could potentially meet inclusion.

The MEDLINE search yielded twenty-three articles, of which none presented case reports or series of the abscopal effect in HNSCC. Google Scholar identified a single case report, and an additional case report was found upon reference searches of relevant abscopal effect reviews.

This manuscript was prepared in accordance with the CARE guidelines for the reporting of case reports¹². Individual informed consent was granted by the patient for dissemination of case details.

CASE DESCRIPTION

The patient was an otherwise healthy 57-year-old man with past medical history significant for hypertension. He was a lifetime nonsmoker, and he drank alcohol occasionally. The patient presented with acute left upper eyelid ptosis and 3-week history of facial pain, mild nasal discharge, and congestion. Initial computed tomography (CT) imaging showed opacification of the left frontal sinus and ethmoid sinuses. There was destruction of the left superomedial orbital wall, with projection of a lobulated soft-tissue mass into the orbit causing displacement of the globe inferomedially. There was erosion of the posterior table of the left frontal sinus and lamina papyracea, without intracranial involvement (Figure 1).

Biopsies obtained during endonasal endoscopic surgery at this time revealed poorly differentiated non-keratinizing squamous cell carcinoma (SCC). The patient was reviewed at the multidisciplinary tumour board, and primary surgical treatment of the tumour with adjuvant therapy was thought to offer the highest probability of oncologic control. Subsequently, the patient underwent craniofacial resection with en bloc removal of the left superomedial orbit, frontal and ethmoid sinuses, medial maxilla, and cribriform plate. As there was no evidence of regional nodal involvement on CT imaging or integrated positron emission tomography–CT (PET-CT), lymphadenectomy was not pursued. Surgical margins were negative

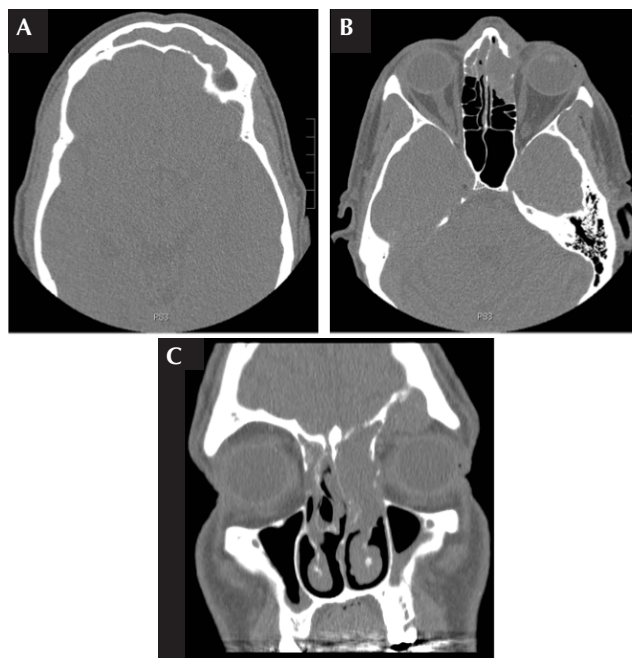


FIGURE 1 Patient's computed tomography imaging on initial presentation. (A) Axial image demonstrating opacification of the frontal sinus, with erosion and partial bone destruction involving the anterior and posterior tables of the left frontal sinus, creating microperforations to the anterior cranial fossa. (B) Axial image demonstrating erosion of the left lamina papyracea. (C) Coronal image demonstrating inferomedial displacement of the left globe from tumour mass extension into the orbit.

following the procedure, and the tumour was staged as pT4a. However, a close margin necessitated concurrent adjuvant chemoradiotherapy with 66 Gy over 33 fractions to the local site alongside 3 cycles of high-dose cisplatin administered as 100 mg/m² intravenously every 21 days concurrent with radiotherapy.

Follow-up PET–CT imaging 4 months following primary treatment revealed a new fluorodeoxyglucose-avid, solitary 9 mm pulmonary nodule in the right lower lobe [Figure 2(A)]. Thoracic surgery consultation was sought, and the patient underwent an open right lower lobe segmentectomy and subcarinal nodal dissection for diagnostic and therapeutic purposes. The pathology was consistent with metastatic SCC, with pleural lymphatic invasion, and negative margins.

Given distant metastatic progression less than 6 months after completion of treatment, the patient was diagnosed with platinum-refractory metastatic HNSCC. Restaging CT imaging demonstrated 2 newly enlarged left cervical lymph nodes [Figure 2(B)], 2 additional new pulmonary nodules, and new pleural nodularity in keeping with further metastatic disease. Based on this, he began systematic therapy with nivolumab, 480 mg fixed-dose treatment infused intravenously every 4 weeks.

The patient tolerated immunotherapy well, his only notable toxicity being initial hyperthyroidism progressing rapidly to hypothyroidism requiring levothyroxine replacement. The initial response to nivolumab was a prolonged period of asymptomatic and stable disease in

the known multifocal sites of metastatic disease, until oligoprogression was observed after more than 1 year of treatment. At that time, CT demonstrated worsening left-sided pleural plaques with a new associated effusion, a newly enlarged 2 cm subcarinal lymph node, and an

extraconal intraorbital lesion suggestive of metastasis (Figure 3).

The intraorbital mass was determined to be vision-threatening, and stereotactic radiotherapy was planned and administered urgently to prevent impending

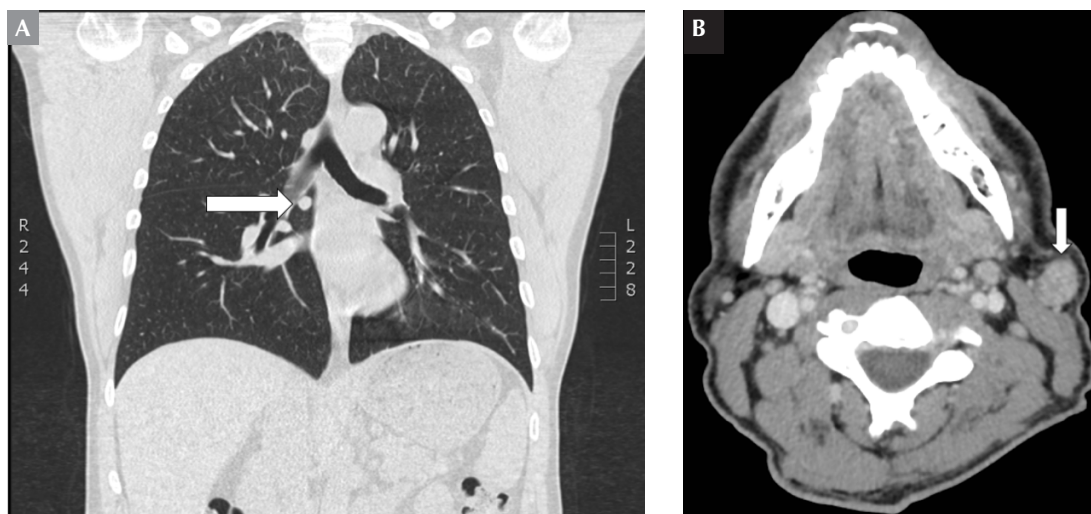


FIGURE 2 Computed tomography evidence of recurrent disease. (A) Coronal image demonstrating a new right pulmonary nodule measuring 9 mm (arrow). (B) Axial image demonstrating a 1.4 cm lesion inferior to the left parotid gland (arrow).

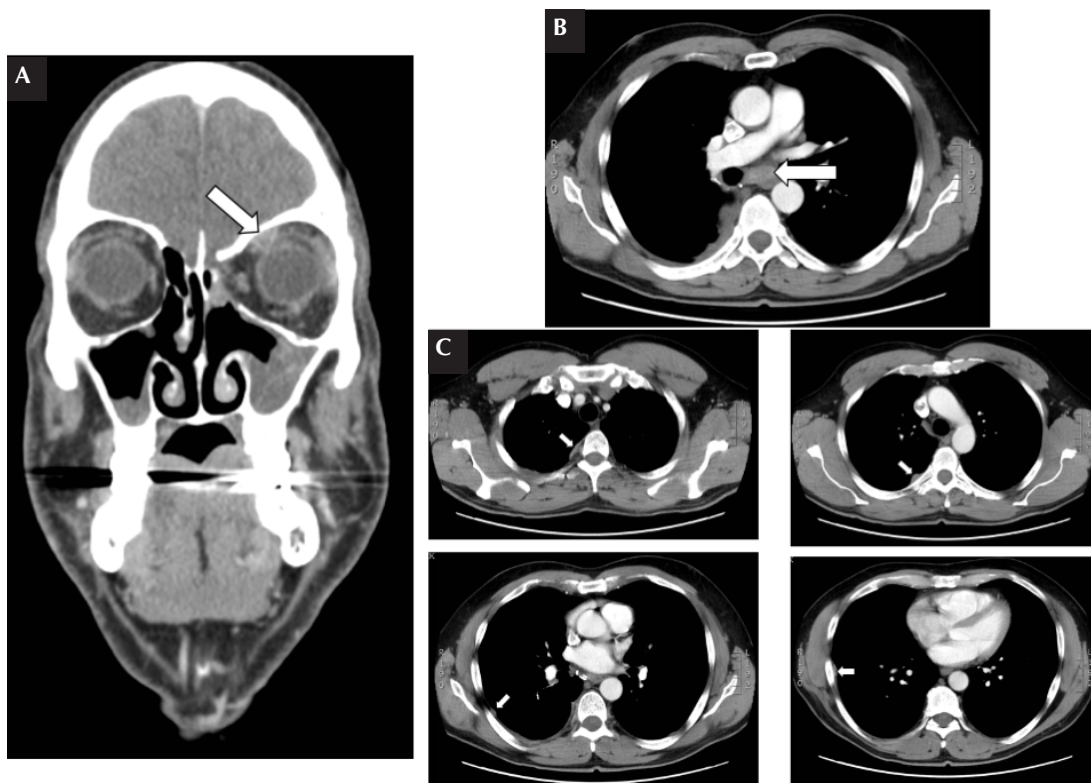


FIGURE 3 Computed tomography images demonstrating oligometastatic progression. (A) Coronal image of a new intraorbital lesion measuring 0.9x1.0x0.7 cm, adjacent to the anterior aspect of the superior oblique muscles (arrow). (B) Axial image of a new enlarged subcarinal node, measuring 1.2x2.8 cm (arrow). (C) Four axial images demonstrating pleural plaques (arrows).

symptoms. Using a stereotactic radiation therapy protocol, 30 Gy in 5 fractions was prescribed to the 90% isodose line (Figure 4). The maximum dose within the target volume was 101.7% to the planning target volume, accounting for a 2 mm expansion from the clinical target volume. Treatment was tolerated well by the patient, despite the sum of total radiation doses exceeding normal tissue tolerance. Nivolumab monotherapy was continued during the time that radiotherapy was planned and administered.

Repeat imaging 1 month following radiotherapy showed significant tumour response of the intraorbital mass. Interestingly, non-irradiated metastatic disease within the thorax also showed significant improvement, including complete resolution of pleural nodularity and associated pleural effusion, resolution of multiple parenchymal nodules, and resolution of subcarinal lymphadenopathy. This response was felt to be in keeping with an abscopal effect, and nivolumab monotherapy was continued. Follow-up imaging 5 months later again showed stable disease, with no evidence of progression at locoregional or distant sites, and no major radiotherapy or immunotherapy toxicities.

DISCUSSION

This is the 3rd reported case of the abscopal effect in metastatic HNSCC. In this case, a patient with sinonasal SCC had metastatic recurrence despite primary combined-modality treatment and showed oligometastatic progression while on nivolumab immunotherapy. With the addition of palliative radiotherapy to prevent impending symptoms at a single site of progression, the ensuing abscopal effect generated a sustained response in metastatic disease outside the radiotherapy field.

Radiotherapy is known to have a dual effect on the immune system. Traditionally, radiotherapy was thought to be immunosuppressive, as demonstrated by the development of lymphopenia, the downregulation of antigen

presenting cell (APC) co-stimulatory molecules, the release of transforming growth factor beta, and the increased infiltration of regulatory immune cells^{13–17}. However, more recent evidence suggests that radiotherapy may in fact have immunogenic effects and be capable of immune system activation¹⁸.

Radiotherapy is capable of altering the tumour microenvironment. Through radiation-induced release of cytokines, infiltration of leucocytes, and alteration of tumour cell susceptibility, radiotherapy is capable of enhancing the immune system's ability to combat malignant cells¹⁸. Radiotherapy induces type I interferon, allowing for activation of dendritic cells and T cells. In turn, type II interferon (γ) is released, causing upregulation of major histocompatibility complex I (MHC I) and an increased presentation of tumour antigens to APCs. The cytokines and chemokines released through radiotherapy also result in a pro-inflammatory state and increased leucocyte infiltration including cytotoxic CD8+ T cells, natural killer cells, and macrophages. Alongside this infiltration, radiotherapy is capable of activating DCs and facilitating their migration to draining lymph nodes. Lastly, radiotherapy increases tumour cell susceptibility to immune system destruction through increased MHC I and Fas expression. Increased presentation of tumour antigens to APCs via MHC I allows for more robust T cell activation and related tumour death, and Fas is essential for T cell-mediated death. For a full review of radiotherapy and the immune system's interplay, see the review by Liu and colleagues¹⁸.

It is through the alteration of the immune system that radiotherapy is thought to exert its abscopal effects. The abscopal effect, from the root words *ab* and *scopos* meaning "position away from" and "target," is the radiotherapy-induced reduction of tumour burden outside the radiotherapy target¹⁹. First described by Mole and colleagues in 1953, the abscopal effect has been variably described throughout the literature²⁰. Through the radiotherapy-mediated

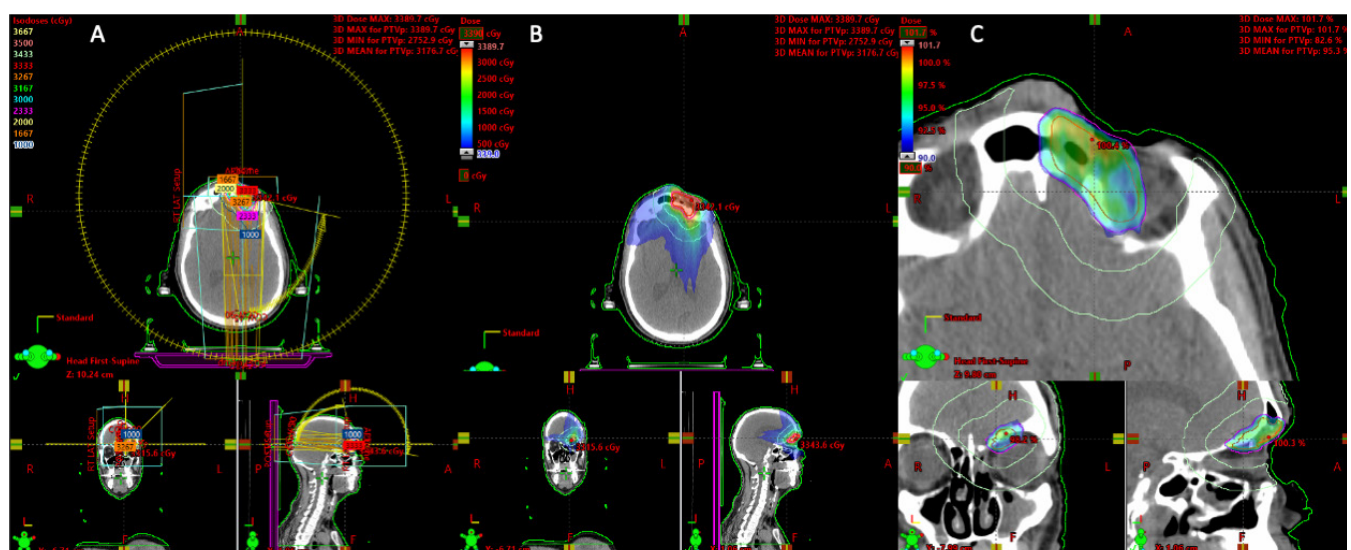


FIGURE 4 Palliative radiotherapy treatment plan. (A) Volumetric arc therapy plan showing Rapid Arcs arrangement and isodose lines. (B) Full dose distribution with colour wash. (C) Zoomed plan highlighting 90% isodose line and planning treatment volume. Prescribed dose of 30 Gy in 5 fractions to 90% isodose line.

destruction of tumour cells already described, the ensuing release of tumour neoantigens into the tumour microenvironment acts as an *in situ* vaccine. Activated T cells home to tumour cells throughout the body—both where the radiotherapy was targeted and to distant metastatic disease¹⁸.

Likely due to both the dual effect of radiotherapy on the immune system and the ability of cancer to evade immune detection, the occurrence of the abscopal effect is rare. Only 46 cases were described between 1969 and 2014, with the majority being primary tumours outside the head and neck²¹. However, with the recent development of immunotherapeutic agents such as nivolumab that reduce the inhibitory effects on the immune system, it has been proposed that the annual number of observed abscopal effects will increase^{18,22}.

The addition of immunotherapy theoretically facilitates the mechanism of the abscopal effect, helping overcome the dual effect of radiotherapy and cancer immune evasion. It is believed that the sequence of treatment may play an important role, with immunotherapy preferentially leading the way²³. The intensity of radiotherapy may also play a role, with stronger radiotherapy doses resulting in an increased likelihood of observing an abscopal effect. In the presented case, 30 Gy in 5 fractions was delivered, equating to 6 Gy per fraction, potentially contributing to a greater chance of producing an abscopal effect²⁴. Finally, although necessary for primary treatment of many forms of head-and-neck cancer, surgical resection of the primary tumour and regional lymph nodes might reduce neoantigen availability, thereby decreasing the potential for an abscopal effect in the future.

Two cases of the abscopal effect on metastatic HNSCC have been described. Shinde and colleagues reported a human papillomavirus-associated oropharyngeal cancer presenting with locoregionally advanced and distantly metastatic¹⁰. The patient received concurrent ipilimumab and nivolumab and showed progression of disease at all sites. Due to increasing symptomatology, the patient underwent palliative radiotherapy²⁵. Notably, no radiation was targeted to the lung disease, and both ipilimumab and nivolumab were continued during radiotherapy. Follow-up at 2 weeks post-radiotherapy demonstrated decreased disease burden at all sites, highlighting an abscopal effect.

The abscopal effect was also described by Yazici *et al.* in a patient with poorly differentiated carcinoma¹¹. Initial treatment included radical locoregional resection followed by adjuvant chemoradiotherapy. The patient had continued locoregional and distant disease progression despite the addition of second-line chemotherapy. Treatment with pembrolizumab offered partial response, but continued disease progression prompted hypofractionated stereotactic radiotherapy with 24 Gy in 3 fractions. Continued immunotherapy and additional hypofractionated stereotactic radiotherapy resulted in a complete response to all lesions, demonstrating a full abscopal effect.

SUMMARY

The currently presented case is the first case of the abscopal effect in a patient with metastatic HNSCC treated with palliative radiotherapy concurrent with single-agent nivolumab immunotherapy, and only the 3rd documented instance of

the abscopal effect in HNSCC to date. In a patient demonstrating oligometastatic progression while treated with nivolumab, the addition of palliative radiotherapy resulted in a dramatic, sustained reduction in disease burden. We also offer the first systematic review of the abscopal effect in metastatic HNSCC and highlight two important cases. The presented case also highlights the potential important role dual treatment with immunotherapy and radiotherapy may play in the treatment of metastatic HNSCC.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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