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CASE REPORT

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Radiation therapy induces an abscopal effect and upregulates programmed death-ligand 1 expression in a patient with non-small cell lung cancer

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Abstract

Radiation therapy (RT) activates the antigen presentation of dendritic cells and priming of cancer-specific cytotoxic $CD8^+$ T cells, occasionally resulting in a systemic immune response to the tumor outside of the treatment field. The phenomenon of tumor regression at the site distant from irradiated fields is known as the abscopal effect. Several case reports have indicated a potential role of RT in overcoming primary and acquired resistance against immune checkpoint inhibitors in non-small cell lung cancer (NSCLC) and melanoma patients. We herein report an NSCLC patient who developed acquired resistance to an RT-induced abscopal effect and subsequently experienced reactivation of the systemic antitumor immune response by pembrolizumab, an antiprogrammed death 1 antibody. In this case, RT not only induced an abscopal effect but also upregulated the programmed death-ligand 1 expression outside of the irradiated field when the patient developed resistance to the abscopal effect. This case can facilitate our understanding of the mechanism underlying the RT-induced systemic immune response against cancer cells and adaptive resistance mechanism of cancer cells from immune surveillance. These findings highlight the promising results of current clinical trials combining RT and immune checkpoint inhibitors. Ongoing clinical trials will further establish evidence supporting combination therapy with RT and immune checkpoint inhibitors.

KEYWORDS

abscopal effect, immune checkpoint inhibitor, non-small cell lung cancer, programmed death-ligand 1, radiation

INTRODUCTION

Radiation therapy (RT) is the main treatment modality for lung cancer and induces local tumor regression and symptomatic relief in lung cancer patients.[1,2] Localized RT activates systemic immune response to cancer cells through activating antigen presentation by dendritic cells (DCs) and priming of cancer-specific cytotoxic $CD8^+$ T cells (CTLs), occasionally resulting in distant responses in tumors outside of the treatment field.[3] The phenomenon of tumor regression at sites distant from irradiated fields is known as the abscopal effect.[4] However, an RT-induced abscopal effect sufficient to control metastatic sites is extremely rare, and clinical cases of the abscopal effect have only been reported in a few types of cancer, including non-small cell lung cancer (NSCLC).[5] In addition, there are few reports concerning changes in programmed death-ligand 1 (PD-L1) expression after RT at the site of the abscopal effect in clinical practice.

We herein report an NSCLC patient who developed acquired resistance to an RT-induced abscopal effect and

subsequently experienced reactivation of the systemic antitumor immune response by antiprogrammed death 1 (PD-1) antibody.

CASE REPORT

A 67-year-old woman with a former smoking habit presented with right shoulder and lower limb pain. Computed tomography (CT) revealed a solitary mass in the upper lobe of the left lung (Figure 1a) with multiple lymphadenopathy and multiple osteolytic lesions. Magnetic resonance imaging revealed multiple brain metastases. Biopsy samples from the tumor in the left lung revealed undifferentiated carcinoma with positive expression of cytokeratin AE1/AE3 and negative expression of TTF-1 and p40. Although the immunohistological findings were not typical of primary NSCLC, no other primary lesions were detected by a thorough systemic investigation, so the patient was diagnosed with clinical stage IVB (cT4N3M1c) NSCLC. *Epidermal growth factor receptor* activating mutations and *anaplastic lymphoma kinase* fusion genes were not observed.

The patient received palliative RT to the thoracic and lumbar vertebrae, the right scapula, and the whole brain at a dose of 30 Gy in 10 fractions for each lesion. On follow-up CT taken 3 months after the initiation of radiotherapy, tumors in the nonirradiated regions, including the left upper lobe, had dramatically decreased without systemic therapy for NSCLC (Figure 1b). This result was considered to be due to an abscopal effect induced by palliative RT for the metastatic sites. However, the primary tumor in the left upper lobe had grown at 26 months after the initiation of RT (Figure 1c). During the 26 months of follow-up, the patient did not receive any systemic therapy for NSCLC, including cytotoxic chemotherapy, molecular-targeted therapy, immune checkpoint therapy, and complementary and alternative therapies.

Subsequently, we performed a rebiopsy of the tumor in the left upper lobe and confirmed findings of undifferentiated carcinoma similar to those from the first biopsy specimen (Figure 2a, d). Interestingly, the PD-L1 tumor proportion score (TPS) increased from 30% in the initial biopsy sample to 100% in the second biopsy sample (Figure 2b, e). Furthermore, the number of CTLs also increased in the tumor tissue of the second biopsy sample compared to the initial biopsy sample (Figure 2c, f). These findings suggest that PD-L1-expressing cancer cells might have caused CTL exhaustion and acquired immunological resistance to the RT-induced abscopal effect. Thereafter, the patient received the PD-1 antibody pembrolizumab. The CT images taken after three courses of treatment showed a partial response, and the patient is still alive with a progression-free survival time of 8 months (Figure 1d).

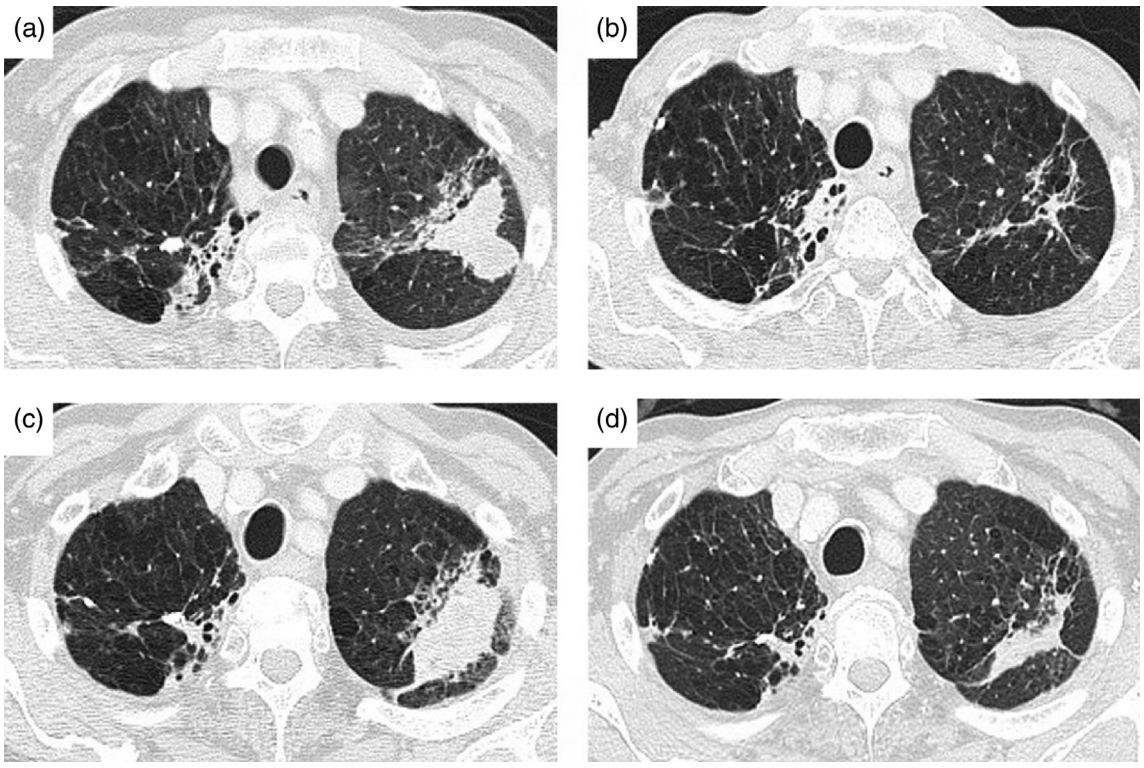

FIGURE 1 Chest computed tomography (CT) scans of the tumor in the left upper lobe. (a) CT scan before the initiation of palliative radiation therapy (RT) to the metastatic sites. (b) CT scan taken three months after the initiation of RT showed a reduction in the tumor size at the nonirradiated region. (c) CT scan taken 26 months after the initiation of RT showed regrowth of the tumor. (d) CT scan taken after three courses of pembrolizumab showed a partial response to the treatment

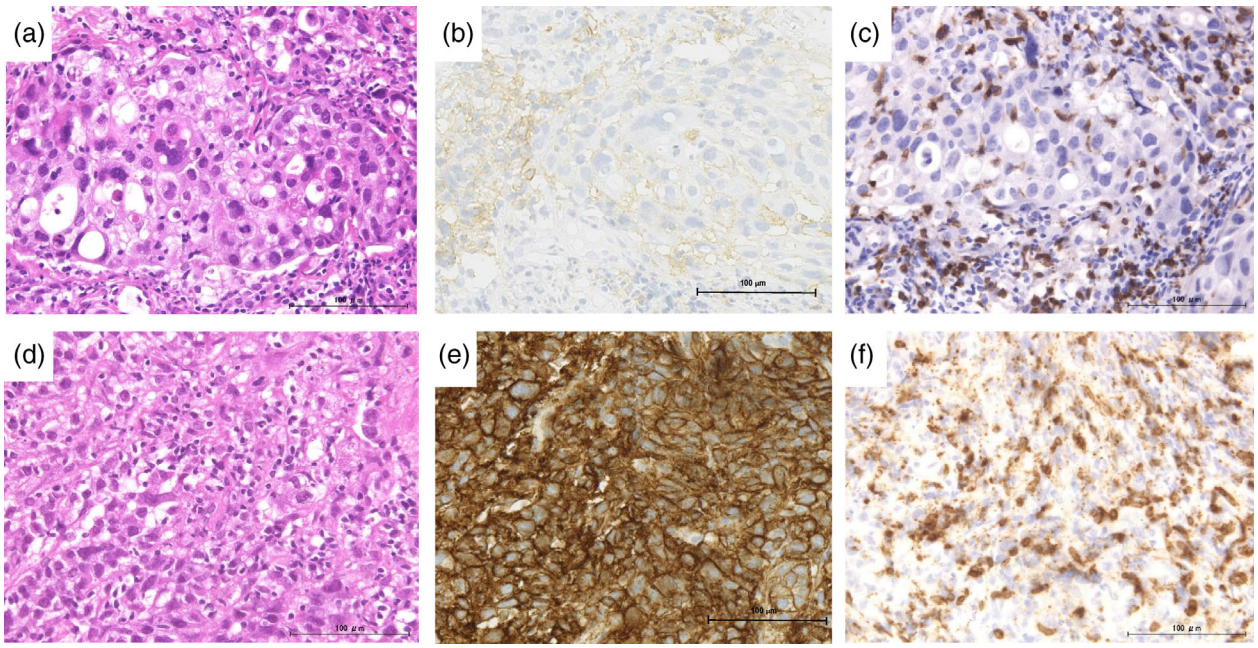

FIGURE 2 Histological findings of the tumor in the left upper lobe. The tumor at the initial biopsy (a, b, c) and second biopsy (d, e, f) is shown. Scale bar, 100 μm. (a) (d) Hematoxylin and eosin staining. (b) (e) The expression of programmed death-ligand 1 (PD-L1) in the tumor cells was assessed using anti-PD-L1 antibody (clone 22C3). (c) (d) The number of tumor-infiltrated cytotoxic $CD8^+$ T cells was assessed using anti-CD8 antibody

DISCUSSION

RT has historically been considered to induce immunosuppressive effects in patients by reducing hematopoietic cells; however, recent studies have shown that RT elicits immune-mediated tumor regression.[6] The damaged double-strand DNA in the cytosol of irradiated cancer cells stimulates the production of interferon type I (IFN-I) and the transcription of interferon-stimulated genes in cancer cells.[5] These secreted factors from cancer cells elicit the recruitment and activation of tumor-residing Batf3 DCs and promote cross-presentation of tumor-derived antigens released from irradiated cancer cells to CTLs by DCs at the tumor-draining lymph node.[7] Other damage-associated molecular patterns released from irradiated cancer cells, including plasma membrane-exposed calreticulin, high-motility group protein B1 and ATP, also promote antigen processing and cross-presentation by DCs and priming of CTLs through the secretion of interleukin-1β (IL-1β) from phagocytes.[8] Subsequently, these cancer-specific CTLs migrate to the distant tumors and eliminate cancer cells, resulting in the abscopal effect.[5] Thus, CTLs are a major effector cell type responsible for the abscopal effect. In our patient, the increment of CTLs in the second biopsy sample suggested that palliative RT for the metastatic sites might have induced priming and migration of cancer-specific CTLs and subsequently induced an abscopal effect at the left lung.

The incidence of an abscopal effect sufficient to induce the regression of metastatic disease is extremely rare, and most patients experience acquired resistance to the abscopal effect within a few years.[5,8] A preclinical study indicated that transforming growth factor-β (TGF-β) in the tumor microenvironment (TME) converted CTLs to the exhausted phenotype and attenuated the RT-induced abscopal effect.[9] The characteristics of exhausted CTLs in the TME are impaired cytotoxicity, reduced proliferation and decreased production of cytokine, thereby resulting in immune escape of cancer cells from the CTL-based immune response.[10] Cancer cells, regulatory T lymphocytes, myeloid-derived suppresser cells, tumor-associated macrophages and plasmacytoid DCs are major cell populations associated with CTL exhaustion in the TME, and inhibitory cytokines, including IL-10 and TGF-β, the metabolic condition and hypoxia also contribute to CTL exhaustion in the TME.[10]

An increased expression of inhibitory receptors, including PD-1, is also the hallmark of exhausted CTLs.[10] Another preclinical study indicated that interferon-γ (IFN-γ) produced from CTLs upregulated the expression of PD-L1 on tumor cells, and the negative regulation of CTLs through PD-L1/PD-1 interaction subsequently led the patient to acquire resistance to the abscopal effect.[11] In addition to IFN-γ, IFN-I and other inflammatory or immunosuppressive cytokines, such as IL-17, TNF-α, IL-1β, IL-6, IL-12 and TGF-β, can also differentially regulate the PD-L1 expression on both cancer and immune cells.[12,13] In our patient, the increment of CTLs and increased expression of PD-L1 on cancer cells in the second biopsy sample indicated that the inflammatory cytokine produced from accumulated CTLs upregulated the PD-L1 expression on lung cancer cells. Subsequently, PD-L1-expressing cancer cells might have induced CTL exhaustion through PD-L1/PD-1 interaction, resulting in acquired resistance to the abscopal effect.

Therefore, treatment with anti-PD-1 antibody successfully reactivated the exhausted CTLs and elicited tumor regression.

Subsequent treatment with an immune checkpoint inhibitor, such as durvalumab or pembrolizumab, after RT has demonstrated a significant benefit for the progression-free and overall survival of NSCLC patients.[14,15] These results support a synergistic effect of combination therapy with RT and immune checkpoint inhibitors. Several clinical trials exploring RT combined with concurrent or sequential immunotherapy in NSCLC patients are currently ongoing.[16] Furthermore, some case reports have also indicated a potential role of RT in overcoming primary and acquired resistance to immune checkpoint inhibitors in NSCLC and melanoma patients.[17–19]

In conclusion, here, we report a case of the effective use of pembrolizumab against acquired resistance to the RT-induced abscopal effect in an NSCLC patient. In this case, RT not only induced an abscopal effect but also upregulated the PD-L1 expression outside of the irradiated field when the patient developed resistance to the abscopal effect.

CONFLICT OF INTEREST

HN has received speaker fees as honoraria and research grant funding from MSD K.K., outside the submitted work. YN has received research speaker fees as honoraria from MSD K.K., outside the submitted work. The other authors have declared no conflict of interest to disclose.

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