Extracranial Abscopal Effects Induced by Brain Radiation in Advanced Lung Cancer

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Abstract: An extracranial abscopal effect induced by central nervous system (CNS)-radiation therapy is considered an unusual event because of the belief that brain has a distinctive immune microenvironment. Regular immune responses from radiation therapy or other interventions were thought to be very limited in the CNS. In addition, CNS autoimmunity and neurodegeneration were presumed automatic consequences of immune cell encounters with CNS antigens. Moreover, the traditional assumption is that nascent tumor-associated antigens produced by radiation therapy could not pass through the blood-brain barrier back into the rest of the body to modulate the immune system and induce extracranial abscopal responses. Emerging data from a small number of case series and individual case reports of various malignancies have radically altered our earlier understanding by revealing that the CNS is neither isolated nor passive in its interactions with the body's immune system. Furthermore, current data indicate that the CNS is both immune-competent and interacts actively with the peripheral immune system. Therefore, radiation treatment to ≥ 1 location of CNS metastases can induce abscopal responses in tumors away from the treated CNS metastatic sites. These observations suggest the abscopal effect traverses the blood-brain barrier. In this article, we reviewed and assessed the clinical evidence of extracranial abscopal responses of CNS-radiation therapy in patients with advanced lung cancer.

Key Words: abscopal effect, brain metastasis, central nervous system lesions, immune response, radiation oncology, thoracic cancer

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Radiation therapy plays a crucial role in the treatment of malignant tumors. Over 60% of all newly diagnosed cancer patients receive radiation therapy with curative intent or in a palliative setting.[1–3] Conventionally, external beam radiation therapy has been administered in multiple small daily doses over several weeks to control tumor growth effectively. However, innovations in radiation technologies have allowed the delivery of highly conformal radiation beams with increased precision while sparing the adjacent normal tissue. In addition to this, the advent of sophisticated imaging methods together with novel radiation devices has led to the development of 3-dimensional conformal radiation therapy, which uses 3-dimensional–based beams to deliver higher doses of radiation.

Ionizing radiation has long been used for the treatment of various malignant tumors because rapidly growing tumor cells are more sensitive than normal cells to DNA damage induced by radiation. Steel and colleagues[4] described the 5 "R's" of radiation biology (repair, repopulation, redistribution, reoxygenation, and radiosensitivity) that are critical to summarize the therapeutic goals of radiation therapy, specifically to maximize the anticancer effects on tumors while minimizing toxic effects on surrounding healthy tissue.[5] Despite these significant advances, the mechanisms of tumor cell death caused by radiation therapy and the possible clinical implications is beginning to be better understood. The appreciation of the complex interactions among radiation-induced tumor cell death, tumor microenvironment, and immune system activation is emerging more clearly. In this investigation, we describe the clinical evidence of not only how local radiation therapy can lead to tumor growth control outside the local irradiated field but also whether it can produce extracranial antitumor effects especially in lung cancer patients with brain metastases.

RADIATION THERAPY AND ABSCOPAL EFFECTS

Conventionally, the antitumor effects of radiation therapy were regarded as immunosuppressive. Radiation therapy is a localized treatment utilizing ionizing photon, proton or electron radiation, that damages the DNA leading to tumor cell death.[6,7] However, it is becoming increasingly evident that radiation may have several potent immunomodulatory effects that can sensitize the immune system against tumors, making them more responsive locally and systemically to its treatment.[8–11] In fact, a number of recent studies reported on the immunomodulating effects of radiation therapy that stimulates the local immune system and ultimately alters the tumor microenvironment.[8–10,12] These alterations in the microenvironment then prompt a reactivation of the immune response. This phenomenon is known as "*abscopal effect*" (*ab scopus*, away from the target) of radiation therapy.[13] The abscopal effect of radiation was originally described by Mole in 1953.[14] He noted that localized radiation targeted at a malignant tumor triggered systemic antitumor effects. This is also referred to as the "*distant bystander effect*," and implies that radiation therapy not only has a localized action on the target tumor tissue but also an out of field systemic antitumor effect. Although observations consistent with the abscopal effect were rare, there are several reasons for the growing interest in this phenomenon. Among these, the prominent motive is the increasing use of radiation therapy in conjunction with gene-targeted and immunotherapy.

Although the complex mechanisms behind this phenomenon is yet to be fully established, immune-mediated cell death appears to play a critical role in producing abscopal responses by radiation therapy (Fig. 1). It is believed that the off-target effects of radiation at nonirradiated distant tumor sites are mediated by tumor antigen primed T lymphocytes (T cells) that travel to metastatic sites and promote tumor regression. It is hypothesized that radiation leads to the liberation of tumor antigens and the production of damage-associated molecules, which lead to the maturation of dendritic cells and T-cell priming in an immunogenic context.[12] In this process, the release of tumor antigens act as proinflammatory mediators,

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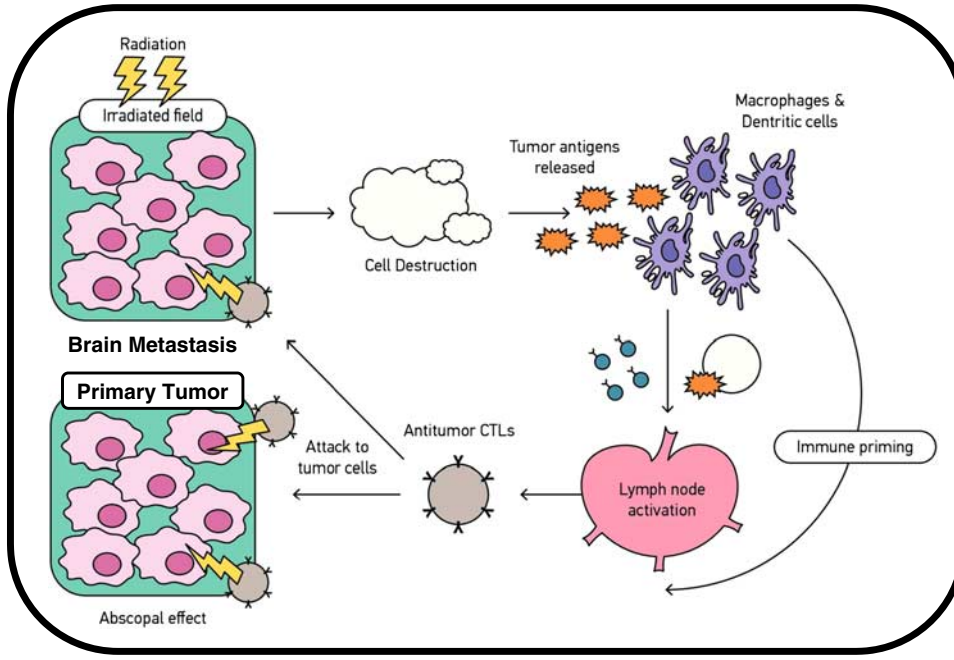

FIGURE 1. Schematic drawing of the mechanism of the central nervous system radiation–induced extracranial abscopal effect in advanced lung cancer with brain metastasis. Radiation of the metastatic lesion causes tumor cell destruction and initiation of the immune process by liberating tumor antigens and producing damage-associated molecules, which lead to the maturation of dendritic cells and improved priming and activation of effector cytotoxic T lymphocytes (CTLs). Tumor antigens also act as proinflammatory mediators, stimulating monocyte production of the cytokines tumor necrosis factor, interleukin (IL)-1, IL-6, and IL-8. These cytokines together with the activated CTLs facilitate tumor cell elimination by attacking not only the tumor bulk in the irradiated area but also travel to nonirradiated sites and promote tumor regression or elimination, a process known as an abscopal effect.

stimulating monocyte production of the cytokines such as tumor necrosis factor, interleukin (IL)-1, IL-6, IL-8, and other signaling molecules. These cytokines and signaling molecules alter the tumor microenvironment and promote the influx of immune cells to lesion sites through antigen-presenting cells that specifically recognize tumor-specific antigens released by the dead cells. Collectively, these events promote tumor cell elimination by primed T cells. Thus, the induction of an abscopal effect by radiation therapy requires sufficient T cells for the activation of the immune system followed by adequate production and presentation of tumor-associated antigen by antigen-presenting cells to T cells, which then produce specific killer T cells for the cancer cells at primary and metastatic locations.[15]

The relative importance of these alterations caused by radiation in the tumor microenvironment are not fully understood, however, it is believed that the immune system senses this damage and triggers immune response pathways resulting in several areas of systemic stimulation.[16] Radiation therapy can produce epitope spreading, thereby increasing the diversity of the T-cell receptor repertoire of intratumoral T cells and broadening the antitumor response.[17] This can induce and improve an immune response specific to the tumor cell.[18] Thus, an improved understanding of the abscopal effects of radiation therapy and its immunologic correlates has implications for the synergistic use of radiation therapy and immunotherapy for the treatment of advanced cancers.[19] There is, particularly, an increasing evidence for the use of combined radiation therapy and immunotherapy in the treatment of brain metastases, including in those patients who have metastatic lung cancer.

LUNG CANCER AND BRAIN METASTASES

Brain metastasis is a common complication in patients with a wide range of tumors. Of patients with brain metastases, lung cancer is the primary tumor in 40 to 50% of the cases.[20,21] In the United States, the 2018 estimate suggests that there will be 234,000 new cases and 154,000 deaths from lung cancer.[22] Non–small cell lung cancer (NSCLC) accounts for up to 85% of all lung cancer cases,[23,24] and roughly $>70\%$ of patients present with locally advanced or disseminated disease at the time of diagnosis.[25] Brain metastases are the most frequent finding in patients with advanced NSCLC. Over 10% of newly diagnosed patients with advanced NSCLC have brain metastases. The brain metastases risk increases to 50% to 60% during their course of disease if patients harbor mutated genes of epidermal growth factor receptor mutation or anaplastic lymphoma kinase rearrangements.[26,27]

Advances in the detection of smaller asymptomatic lesions using magnetic resonance imaging (MRI) screening and improvement in the overall survival rates has increased the incidence of brain metastases significantly in recent years. Moreover, improvements in imaging technology, delivery of focused radiation therapy, development of novel targeted therapies, innovations in immunotherapy and a better understanding of treatment-related toxicities have also contributed to the evolvement of current trends in the management of brain metastases from lung cancer and other advanced tumors.

EXTRACRANIAL ABSCOPAL RESPONSES

For the better part of the last century, the central nervous system (CNS) has been considered as an almost separate and

immunologically inert organ with immune privilege.[28,29] Specifically, the CNS immune privilege was construed as CNS isolation from the immune system by the blood-brain barrier (BBB), the lack of draining lymphatics, and the apparent immunoincompetence of microglia, the resident CNS macrophage. It was viewed primarily as a tissue of postmitotic cells that were highly vulnerable to the onslaught of activated immune cells, if and when these immune cells infiltrated the CNS. Regular immune responses from therapeutic interventions were thought to be very limited in the CNS. Moreover, CNS autoimmunity and neurodegeneration were presumed automatic consequences of immune cell encounters with CNS antigens. The idea that an extracranial abscopal effect could be induced by radiation therapy to the brain would thus sound particularly unusual due to the traditional belief that the brain has its own distinctive immune microenvironment. It has been assumed that nascent tumors associated antigens produced by radiation therapy did not pass through the BBB.[30] Thus, an extracranial abscopal effect induced by CNS-radiation therapy is particularly considered to be an unusual event because of the brain's distinctive immune microenvironment.

Over the last 2 decades, there has been a dramatic reevaluation of the type of cellular immune responses that can occur within the CNS.[31–33] Emerging data from clinical investigations have radically altered the earlier viewpoint by revealing that the CNS is neither isolated nor passive in its interactions with the immune system.[33] Peripheral immune cells can cross the intact BBB, CNS neurons and glia actively regulate macrophage and lymphocyte responses, and microglia are immunocompetent but differ from other macrophage/dendritic cells in their ability to direct neuroprotective lymphocyte responses. Furthermore, current data indicate that the CNS is both immune-competent and actively interactive with the peripheral immune system. Inflammation is also recognized to be a prominent feature of many neurodegenerative disorders of the CNS. Thus, radiation treatment to ≥ 1 locations of CNS metastases can induce abscopal responses in tumors away from the treated CNS metastatic sites.

BBB AND ABSCOPAL EFFECT INTERACTIONS

The cerebral microvessels and capillaries of the CNS form the BBB. The crucial function of the BBB is to provide a defense against infections and toxins entering the brain via the bloodstream circulation. However, the BBB also poses an obstacle to the delivery of small and large therapeutic molecules to the brain. The tight junctions of the BBB play critical role in preventing large molecules such as neurotoxic plasma components, blood cells, and pathogens from entering the brain. This property arises from the epithelial-like tight junctions within the brain capillary endothelium. Thus, the immune system and the CNS share a unique relationship through the BBB.

To maintain proper neuronal functioning, the BBB regulates the transport of certain small molecules (with a molecular weight < 400 Da and forms <8 hydrogen bonds) into and out of the CNS through a lipid-mediated free diffusion.[34,35] In addition, a variety of differentially expressed carriers and receptor-mediated systems exist which closely control the transport of larger molecules that can be transported through the BBB.[34,35] Moreover, the BBB itself secretes molecules such as cytokines, prostaglandins, and nitric oxide that affect the immunologic signaling.[28]

Passage of immune cells across the BBB depends upon an elaborate interaction between the immune cell and the BBB termed diapedesis. However, this occurs at low rates under physiological conditions.[36] Preclinical studies using a mouse model suggests that a cell-mediated immune response to foreign antigens in the brain cannot be mounted unless the BBB is disrupted.[37] Under normal physiological conditions, various regulatory components of the BBB prevent immunologic mechanisms of the abscopal effect. If there is a low rate at which the immune cells cross the BBB then it is likely that there would be insufficient cells to produce an abscopal response by the radiation therapy. Peptide antigens of a suitable size are required to be presented to T cells and are among the smaller elements that can mediate an abscopal response. However, these peptide antigens cannot diffuse freely across the BBB due to the limitations of their size and solubility.[34] As the transport of larger molecules is tightly regulated by the BBB, the tumor-associated antigens are very unlikely to cross in significant amounts through receptor-mediated transportation.

MODULATION OF BBB PERMEABILITY BY RADIATION

Under normal physiological conditions, the BBB prevents the passage of the immunogenic signaling molecules that are required for the production of the abscopal responses from the intracranial compartments to the extracranial compartments or vice-versa. With the advent of novel radiation delivering techniques, it is now possible that the endothelial permeability of the BBB can be modulated to facilitate the passage of the immunogenic signaling molecules between the intracranial and extracranial compartments. In healthy regions of the brain, high doses of radiation have been shown to modulate BBB permeability, induce morphologic changes in tight junctions, reduce the cell density, and produce the formation of actin stress fibers in cerebral endothelial cells.

A study evaluating large single doses of radiation on the cerebral microvasculature showed that radiation increases the BBB permeability to fluorescein isothiocyanate-dextran molecules of various sizes.[38] Earlier studies using animal models also have shown that brain radiation increases the uptake of labeled markers.[39] Potential mechanisms for this increased uptake include modulation of the vasculature thereby opening the tight junctions, and increasing the activation of vesicular transport pathways between the intracranial and extracranial compartments.[40–42] In addition, brain radiation also results in an increased expression of a wide variety of acute-phase reactants including tumor necrosis factor α, which modulates the BBB.[43–46]

Clinical evidence that radiation therapy modulates the BBB has been suggested by the detection of increased intracranial concentrations of radiolabeled markers and chemotherapy agents after radiation. For instance, Qin et al[47] found a linear dose-response when measuring uptake of a technetium marker during radiation therapy in patients with brain tumors. These investigators also observed spatial differences in the uptake between regions that received higher or lower doses of radiation and increased levels of methotrexate in the cerebrospinal fluid following radiation therapy.[48] These findings form the basis and provide an explanation for why an abscopal effect traversing intracranial and extracranial compartments can be observed after radiation therapy. It is plausible that radiation therapy not only causes the production of tumor-associated antigens and other immunogenic signaling molecules but also facilitates their release into the extracranial vasculature through the BBB modulation (Fig. 2).

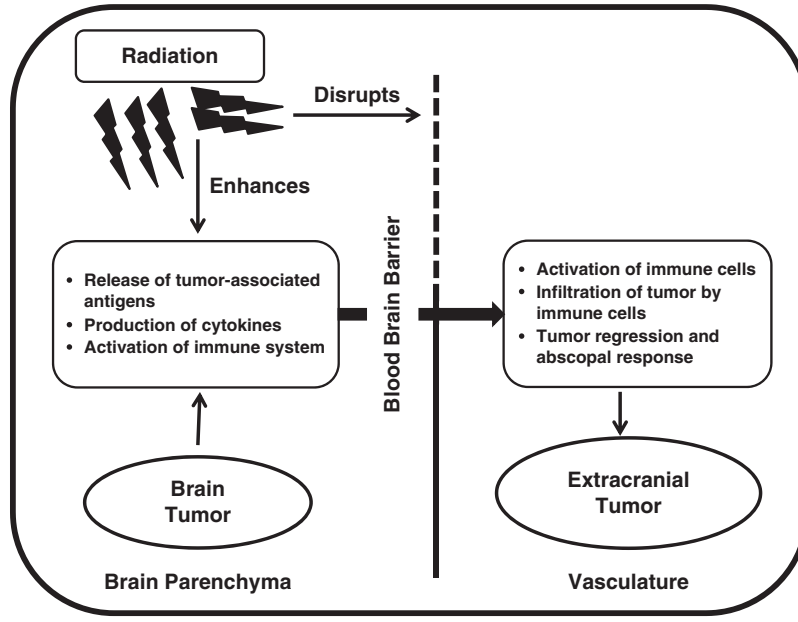

FIGURE 2. Schematic representation depicting the potential interactions between radiation, the blood-brain barrier, and the antitumor immunity. Radiation therapy increases the permeability of the blood-brain barrier allowing the passage of immunogenic signaling from intracranial to extracranial compartments resulting in the abscopal response.

CLINICAL CASES OF EXTRACRANIAL ABSCOPAL RESPONSES IN ADVANCED LUNG CANCER OR TUMORS METASTASIZED TO LUNGS

Clinical evidence of extracranial abscopal responses following radiation treatment to ≥ 1 location of CNS metastases of the advanced lung cancer has been reported only in the form of case reports (Table 1). The clinical outcomes of these reports serve as a basis for the development of innovative approaches for the treatment of CNS metastases of not only advanced lung cancer but also other malignancies with brain metastasis.

Recently, Lin et al[49] reported a case of an extracranial abscopal effect after stereotactic brain radiation therapy as second-line treatment in a patient with lung adenocarcinoma. In this study, a 71-year-old male patient was initially diagnosed with poorly differentiated stage IV adenocarcinoma in the right lobe of the lung. Following 6 cycles of chemotherapy with paclitaxel and nedaplatin, the primary tumor enlarged, indicating the failure of his first-line chemotherapy. The patient underwent immunotherapy with atezolizumab. Although the primary tumor and mediastinal lymph nodes were reduced after the introduction of immunotherapy, the patient developed brain metastasis in the right parietal lobe. Stereotactic radiation therapy using the X-knife was administered to a dose of 48 Gy in 8 fractions and immunotherapy with atezolizumab was continued. Follow-up assessment after 3 months of radiation therapy to brain showed that the nodules in the right lower lung had shrunk and the number of subpleural lesions in the basal segment of the left lower lung had reduced in size. In addition, multiple lymph nodes in the mediastinum had become smaller. These findings indicated the clinical evidence for extracranial abscopal responses following radiation treatment to the CNS metastases of a patient with advanced lung cancer. Further assessment using MRI of the brain revealed that the primary metastases in the parietal lobe had disappeared. However, multiple other metastases and peritumoral edema emerged in the right frontal lobe and left cerebellar hemisphere. These new intracranial metastatic lesions regressed after continued radiation therapy. Overall, these findings suggest that combining brain radiotherapy with immunotherapy can induce an extracranial abscopal response in patients who have advanced lung cancers with brain metastasis.

Hamilton et al[50] reported an extracranial abscopal effect after radiosurgery for a solitary brain metastasis in a patient with advanced NSCLC. A 47-year-old male initially presented

TABLE 1. Clinical Cases of an Extracranial Abscopal Responses Following Radiation Therapy for Brain Metastases in Advanced Lung Cancer

Sex	Age (y)	Modality of Radiation Therapy	Radiation Dose	Systemic Therapy	Location of Extracranial Abscopal Response	References
Male	71	Stereotactic radiation	48 Gy in 8 fractions	Atezolizumab	Lung	Lin et al[49]
Male	47	Stereotactic radiation	25 Gy in 5 fractions	None	Lung	Hamilton et al[50]
Female	71	Whole-brain radiation	30 Gy in 10 fractions	None	Lung*	Chuang et al[51]
Male	63	Whole-brain radiation	45 Gy in 15 fractions	None	Lung	Katayama et al[52]
Male	60	Stereotactic radiation	Not reported	None	Lung, adrenal, and liver	Yarchoan et al[53]

*The metastatic lung tumor that had extracranial abscopal response following radiation therapy was a metastasized tumor from a metastatic adenocarcinoma of colorectal cancer.

with right groin and lower-extremity numbness with an unremarkable review of his other systems. The patient had a past medical history including aorto-occlusive disease status post–femoral-popliteal bypass, peripheral artery disease, coronary artery disease, and tobacco dependence. Because of an aorto-femoral bypass graft occlusion, he was diagnosed with right limb occlusion with critical limb ischemia of the right lower extremity. His computed tomography (CT) angiography of the chest initially revealed a nodule at the left lung apex, slightly cavitary in nature together with a left paratracheal soft tissue density. Before his recommended follow-up visit, 2 months later, the patient was admitted to the emergency room with bilateral chest pain and associated shortness of breath and dyspnea. His repeat CT angiography showed an increase in the left upper lobe mass density and bilateral hilar adenopathy indicating a primary neoplasm with metastatic disease. The patient's biopsy revealed a poorly differentiated non–small cell carcinoma. His positron emission tomography (PET) scan revealed an invasion of the pleura with perivascular and lymphatic metastatic involvement, confirming a hypermetabolic left upper lobe mass. Subsequent MRI of the brain showed a metastatic lesion in the left frontal lobe with surrounding edema. The patient underwent radiosurgery to the solitary brain lesion. A total peripheral dose of 2500 cGy was delivered in 5 fractions. The patient did not receive any form of systemic therapy, such as chemotherapy or immunotherapy. At 1-month follow-up after the initial brain lesion diagnosis, the MRI of the brain showed a reduction in lesion size was observed. His repeat PET/CT 4 weeks post stereotactic radiosurgery treatment revealed no appreciable mass in the left upper lobe. Further follow-up chest CT after 3 and 7 months posttreatment showed complete resolution of the original left upper lobe pleural-based mass. His brain MRI at 7 months' follow-up also showed complete resolution of the solitary metastatic focus in the left frontal region and no evidence of new metastatic disease. Thus, the findings of this case study demonstrated that radiosurgery to brain metastasis can induce a extracranial abscopal response in a chemotherapy and or immunotherapy naive patient with advanced NSCLC.

Chuang et al[51] described a case of an extracranial abscopal response in a chemotherapy-naive patient who had metastatic NSCLC tumor after whole-brain radiotherapy. A 47-year-old female initially presented to emergency services due to unsteady gait and dyspnea. CT imaging of her chest showed a huge mass involving the left main bronchus with total collapse of the left lung. A bronchoscopic biopsy and subsequent immunohistochemistry indicated a metastatic adenocarcinoma from colorectal cancer. In addition, her MRI scan revealed multiple brain metastases. The patient received emergent whole-brain radiation therapy to a dose of 30 Gy delivered in 10 fractions to treat her metastatic brain lesions. Two months postradiation therapy to her brain, her lung mass had markedly regressed indicating the evidence of an extracranial abscopal response from brain radiation.

Katayama et al[52] reported an extracranial abscopal response in a chemotherapy-naive patient with advanced NSCLC following whole-brain radiotherapy. This study included a 63-year-old male patient who initially presented with worsening dysgraphia and memory impairment. His CT and chest radiography revealed a 4 cm solitary tumor in the upper lobe of the left lung with mediastinal lymphadenopathy, and his MRI revealed a 3 cm solitary tumor, assumed to be a metastatic lesion, with cerebral edema extending from the left temporal lobe to the occipital lobe. Bronchoscopic cytology from the lung tumor revealed malignant cells that were consistent with NSCLC. The patient was diagnosed with stage IV NSCLC. The patient underwent a surgical enucleation of the brain tumor as initial treatment due to his rapidly progressive symptoms. The pathologic examination of the excised cranial lesion confirmed it to be a NSCLC metastasis. Despite the surgical excision of the tumor, his brain metastasis progressed rapidly. Therefore, the patient underwent whole-brain radiotherapy plus a boost of radiotherapy to total dose of 45 Gy delivered in 15 fractions to his metastatic brain tumor. The patient also received palliative radiation (30 Gy in 10 fractions) to a third lumbar vertebral metastasis. Seven weeks postradiation therapy to the brain, the tumor in the left upper lobe of the lung and his mediastinal lymph nodes had regressed in size. Moreover, his lung tumor shrank significantly, indicating the extracranial abscopal responses following his radiation therapy. Furthermore, these extracranial abscopal responses occurred after the radiation of the metastatic lesions without systemic chemotherapy or immunotherapy.

Yarchoan et al[53] described a case of an extracranial abscopal response after radiation therapy in a 60-year-old male patient with an oligometastatic NSCLC. The patient initially complained of several weeks of dizziness, headaches, nausea, and vomiting. His MRI showed a multilobulated cerebellar lesion and subsequent immunostaining assessment of his pathology confirmed a diagnosis of lung adenocarcinoma as a primary tumor. A CT scan of his chest revealed 2 speculated masses in the right upper lobe with additional small nodules in the right upper lobe and along the right minor fissures. Several months later, the patient underwent a flexible bronchoscopy, mediastinoscopy, right thoracotomy, and an uncomplicated right upper lobe lobectomy, which confirmed that the patient had primary adenocarcinoma of the lung with distant metastasis to the brain. The patient was administered 4 cycles of cisplatin-based chemotherapy with pemetrexed. His repeat CT scan demonstrated new metastatic lesions in the left adrenal gland, left lower lobe, and in the liver. In addition, his repeat MRI of the brain showed a new right frontal asymptomatic lesion. The patient was then treated with whole-brain radiation and localized stereotactic radiosurgery. Shortly after completing this treatment, his MRI showed a second new right parietal cortex lesion, which was also treated with stereotactic radiosurgery. After completion of his radiation treatment, no evidence of recurrent disease was seen on a restaging CT. His metastatic lesions in the adrenal, lung, and his liver had completely regressed. The patient received no additional therapy for a period of 5 years, and multiple restaging scans have not shown any evidence of recurrent disease. Collectively, these observations demonstrate that brain radiation therapy–induced extracranial abscopal responses in a patient with oligometastatic lung cancer.

CONCLUSIONS

The literature to date describes only a limited number of clinical cases of extracranial tumor regression following radiation therapy for ≥ 1 intracranial metastasis of lung cancer. Although the BBB likely obstructs the abscopal effect from passing between intracranial and extracranial compartments, clinical evidence from these case studies demonstrates that radiation therapy disrupts this barrier and can trigger distant abscopal responses. However, there are methodological challenges that need to be overcome to distinguish true abscopal effects induced by radiation therapy from those of systemic immunotherapy. It is possible to assess the immunomodulatory changes that are necessary to mediate the abscopal effects induced by radiation therapy in the absence of systemic immunotherapy. For instance, measurements of titers of tumor-specific antibodies can provide an evidence for true abscopal

effects after radiation therapy. Thus, when radiation therapy is combined with systemic immunotherapy, it is more difficult to identify if the abscopal responses are from one or the other or both modalities. If the abscopal effect of radiation is understood to be a result of enhancement of the antitumor immune response, then one must effectively distinguish between the outcomes of 2 different immunologic therapies. Among the 5 case reports included in this study, 4 of the cases showed radiation therapy without any concurrent systemic immunotherapy resulted in distant antitumor effects indicating that radiation therapy alone induces the abscopal effects. Although randomized prospective studies can provide a more in-depth understanding of these abscopal responses, such studies may be difficult to conduct due to the rarity of these effects in patients with advanced malignant tumors.

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