Possible Interaction of Anti–PD-1 Therapy with the Effects of Radiosurgery on Brain Metastases

Ahmed K. Alomari¹, Justine Cohen², Alexander O. Vortmeyer¹, Anne Chiang², Scott Gettinger², Sarah Goldberg², Harriet M. Kluger², and Veronica L. Chiang³

Abstract

Delayed radiation-induced vasculitic leukoencephalopathy related to stereotactic radiosurgery (SRS) of brain metastases has been reported to manifest clinically 9 to 18 months after treatment. Immune-modulating therapies have been introduced to treatment regimens for malignancies with metastatic predilection to the brain. The interaction of these systemic therapies with other modalities of treatment for brain metastases, namely, SRS, has not been fully characterized. We report two patients with metastatic malignancies to the brain who received SRS followed by immunotherapy with monoclonal antibodies (mAb) to programmed death 1 (PD-1). Both patients appeared to have early clinical and radiologic progression of their treated lesions, which was highly suspicious for tumor progression. Both patients underwent surgical resection of their lesions and the material was submitted for histopathologic examination. Pathologic examination in both cases showed predominantly radiation-induced changes characterized by reactive astrocytosis and vascular wall infiltration by T lymphocytes. The accelerated response to SRS in these two patients was temporally related to the initiation of immunotherapy. We propose a possible biologic interaction between SRS and the PD-1 mAbs. Additionally, awareness of this potential occurrence is critical for accurate interpretation and proper management of clinical and radiologic findings in these patients.

Introduction

Radiographic changes—unrelated to tumor after stereotactic radiosurgery (SRS) for brain metastasis are well documented (1–5). Classically, these changes manifest clinically months to years after SRS (5, 6). The addition of immune-modulating therapies to systemic treatment paradigms is becoming standard of care in some malignancies that tend to metastasize to the brain, in particular melanoma and non–small cell lung cancer (NSCLC; refs. 7–9). A number of studies have shown activity of immune checkpoint inhibitors in patients with brain metastases, and combinations of these drugs with SRS may be used more frequently in the future (10–12). However, the effects of immunotherapy after SRS on brain tumors and brain tissue adjacent to SRS-treated tumors have not been fully characterized. Programmed death 1 (PD-1) is a human cell-surface coinhibitory receptor expressed on activated T cells that suppresses T-cell effector function when engaged by PD ligand (PD-L1 or PD-L2; ref. 13). PD-1 antagonist antibodies, such as nivolumab and pembrolizumab, can relieve inhibition of antitumor CD8⁺ T cells, resulting in durable clinical and radiographic responses (14). In this report, we describe the clinical, radiologic, and pathologic findings in two patients—one with melanoma and one with NSCLC metastatic to the brain—who were treated with SRS to brain metastases prior to systemic treatment with PD-1 monoclonal antibodies (mAb). In both cases, the time frames for clinical progression and the development of radiologic findings were highly suspicious for tumor progression. However, pathologic examination showed findings consistent with an accelerated response to SRS treatment.

Case Presentation

Case 1

History and clinical course. A 45-year-old woman was initially diagnosed with a 2.3-mm ulcerated melanoma on the dorsum of the right foot in 2008. Her sentinel lymph nodes were uninvolved. In 2010 she presented with an inguinal mass comprising four lymph nodes positive for melanoma that harbored a BRAFV600E mutation. She received adjuvant interferon-α for 12 months and was then found to have lung and brain metastases. She was subsequently treated with a number of systemic therapies between 2010 and 2013, including ipilimumab (anti–CTLA-4), vemurafenib (BRAFV600E inhibitor), carboplatin and paclitaxel (chemotherapy), and dabrafenib and trametinib (MEK inhibition). During that period of time, five brain metastatic lesions ranging in size between 0.3 cm and 0.6 cm were treated with SRS. Three of these lesions were treated before the patient started vemurafenib. The other two were treated while the patient was on vemurafenib. After an initial slight increase in size, these lesions regressed and remained stable at a size approximately similar to their original size. She also remained asymptomatic throughout the entire follow-up period. In 2014, MRI of the brain showed a new lesion in the right anterior temporal lobe measuring 1.3 cm in its greatest dimension. This lesion was also treated with SRS in the form of 22 Gy to the 50% isodose surface. Six weeks
after SRS, the patient developed new-onset seizures that were controlled by levetiracetam. Five months after this last radiosurgical treatment, she started therapy with pembrolizumab at 2 mg/kg/3 weeks. One month later, she reported progressively worsening headaches associated with an increase in seizure frequency not controlled with medical therapy. A repeat MRI showed increase in the size of the enhancing temporal lesion with statistically significant increase in surrounding edema. Given the early timing of the MRI changes, there was concern about progressive tumor growth, and the patient underwent craniotomy for local lesion management. The lesion was resected en bloc. Postoperatively, her headaches and seizures resolved.

**Radiologic examination.** The patient has had multiple brain metastases during the course of her disease. Of interest is the 1.3 × 1.1 × 1.0 cm gadolinium enhancing lesion identified in the right anterior temporal lobe found on surveillance MRI (Fig. 1A and B). Two months after SRS, this lesion had decreased in size to 1.0 cm in its greatest dimension (Fig. 1C and D). One month after the initiation of treatment with pembrolizumab (6 months after SRS), gadolinium-enhanced MRI showed that the temporal lesion had increased in size to 2.0 cm. This change was associated with significant increase in surrounding T2 and FLAIR signal abnormality consistent with perilesional edema (Fig. 1E and F). Postoperative MRI 3 months after surgical resection confirmed resection of the temporal lesion and resolution of right temporal lobe edema (Fig. 1G and H).

**Pathologic examination.** A biopsy of a left occipital brain lesion previously performed to confirm metastatic disease showed a pleomorphic malignant neoplasm staining positive with Melan A and HMB-45, consistent with metastatic melanoma. Histologic examination of the treated anterior temporal lesion, however, showed a central zone of predominantly extracellular melanin pigment and shadows of dying cells with intracellular melanin pigment (Fig. 2A and B), surrounded by a rim of necrosis with no viable tumor cells (Fig. 2C). At the periphery of the necrosis were areas of prominent eosinophilic hyalinization of blood vessel wall and intense vasculitis characterized by infiltration by CD3+ T lymphocytes and CD68+ microglial cells of the vessel walls (Fig. 2D–F). CD20 highlighted rare B lymphocytes, and PD-L1 (E1L3N antibody) showed no staining in lesional tissue. These features were consistent with delayed treatment-related inflammatory changes that have been previously reported post-SRS.

**Follow-up.** The patient restarted pembrolizumab within 2 weeks of surgery and remains headache and seizure free 4 months after surgery. Her last MRI scan 3 months after surgery showed markedly reduced edema in the right temporal lobe and stable appearance of other lesions. She continues surveillance MRI for follow-up.

**Case 2**

**Clinical course.** A 59-year-old woman with smoking history presented with confusion and speech difficulty. MRI of the brain showed a left frontotemporal enhancing lesion. Further workup revealed a right upper lobe lung mass and several enlarged hilar lymph nodes. Mediastinoscopy was performed, and pathology showed poorly differentiated adenocarcinoma of the lung. The brain lesion was therefore presumed to be a brain metastasis and treated with SRS comprising 20 Gy to the 50% isodose surface. One month after SRS, MRI showed that the size of the lesion and perilesional edema had decreased. Systemic therapy was started with nivolumab and ipilimumab on a clinical trial (NCT01454102). Within 2 months of initiation of immunotherapy, extracerebral imaging demonstrated remarkable response to therapy. However, brain MRI showed significant increase in the size of the treated lesion and perilesional edema causing mild midline shift. The patient developed symptoms of intermittent confusion, requiring treatment with steroids, and craniotomy was performed for local lesion control.

**Radiologic examination.** Initial MRI showed a 2.3 × 2.0 cm enhancing mass in the left frontotemporal region. FLAIR
sequence showed marked perilesional edema (Fig. 3A and B). MRI performed 1 month after SRS showed a marked decrease in the size of the lesion (1.4 × 1.2 cm) and mild improvement in the perilesional edema (Fig. 3C and D). MRI 2 months after the initiation of immunotherapy and 3 months after SRS showed that the lesion had regrown (2.7 × 2.3 cm), and the increased perilesional edema was now associated with mild midline shift (Fig. 3E and F). The right upper lobe lung lesion, conversely, showed marked response to immunotherapy, decreasing in size from 5.2 × 4.0 cm before treatment to 3.6 × 2.3 cm after 2 months of treatment. Similarly, several enlarged mediastinal lymph nodes showed reduction in size following therapy. Six-week postoperative brain MRI showed complete resection of the lesion and marked decrease in the amount of perilesional edema with resolution of midline shift (Fig. 3G and H).

Figure 2. A and B, representative hematoxylin and eosin (H&E) sections showing necrotic tumoral tissue with abundant melanin pigment and admixed hemorrhage (>4 and ×20). C, an H&E section of the tissue surrounding the melanin nodule revealing only necrotic material (>20). D and E, the brain tissue further out from the melanin nodule showing marked radiation-induced changes characterized by vascular wall thickening, hyalinization, and lymphocytic infiltration (>10 and ×40). F, CD3 immunostaining highlighting the predominantly lymphocytic nature of the inflammatory infiltrate in the vasculitic lesions (>40).
Pathologic examination. Tissue from the patient's mediastinal lymph node biopsy showed metastatic adenocarcinoma staining positively for CK7 and TTF-1, confirming its lung origin. Molecular profiling showed no genetic alterations in EGFR, ALK, KRAS, or ROS. Pathologic examination of the patient's irradiated left frontotemporal lesion showed a large central area of necrosis with minute foci of residual tumor cells encased within the necrosis (Fig. 4A–C). Surrounding the necrosis was evidence of marked vasculitis, reactive astrocytosis, and hyalinization of blood vessels (Fig. 4D). The blood vessel walls were infiltrated by CD3⁺ T cells and CD68-positive microglial cells (Fig. 4E and F). Similar to the first case, rare B cells were present, and no PD-L1 staining of the lesional tissue was identified.

Follow-up. The patient was able to resume systemic therapy on the clinical trial within 2 weeks of surgery, and she remains asymptomatic neurologically 6 weeks after surgery.

Discussion
Immune checkpoint inhibitors are revolutionizing the ability to treat metastatic cancer (15–18). Many clinical trials are under way using these agents to treat a variety of cancers, and inhibitors of CTLA-4 and PD-1 have been approved for melanoma (19). Pembrolizumab and nivolumab, inhibitors of PD-1, were the first to be approved for melanoma and are being studied in other diseases and in combination with other drugs (nivolumab was recently approved for squamous cells carcinoma of the lung). The interaction between immune checkpoint inhibitors and standard treatments for brain metastases, such as SRS, however, remains underinvestigated (20, 21).

SRS is well established as a treatment modality for brain metastases (22, 23). Although initially intended to minimize the effect of radiation on the whole brain, several reports have now documented that, in a subset of patients, the high focal dose of radiation to the small rim of normal brain surrounding the metastasis can result in a delayed appearance of progressively enlarging gadolinium-enhancing areas surrounding the isocenter of radiation—typically 9 to 18 months after SRS (2–4). Histologic examination of these areas shows a delayed radiation-induced vasculitic leukoencephalopathy (DRIVL), characterized by myelin loss, infiltrating macrophages, marked reactive astrocytosis, and hyalinization and sclerosis of blood vessels. Additionally, these cases consistently showed marked inflammatory changes, including abundant infiltration of CD3⁺ T lymphocytes seen diffusely scattered within the parenchyma and infiltrating vascular walls giving a vasculitis-like appearance (2).

In the two cases presented here, routine MRI follow-up scans showed an initial decrease in the size of the irradiated lesions after SRS, as expected. However, only 1 to 2 months after initiation of immune checkpoint inhibitor treatment, follow-up MRI showed regrowth in the size of the treated lesions with statistically significant increase in perilesional edema-causing symptoms. In the first patient, symptoms developed almost 6 months after the administration of SRS. Although uncommon, it is not impossible to have symptomatic regrowth of lesions—unrelated to tumor recurrence—as early as 6 months after treatment, especially in larger lesions (5). However, given the initial size of the metastatic lesion in this patient, the temporal relationship with pembrolizumab administration, and the more typical delayed development of radiographic and clinical changes following SRS, it is thought that immunotherapy likely played an important role in the pathogenesis of this patient’s post-SRS lesions.

We postulate that immunotherapy may accentuate or accelerate radiation-induced changes in the perilesional brain tissue, especially changes that are immunologically mediated (20). By blocking the interaction between PD-1 and its receptor ligands, PD-L1 and PD-L2, treatment with drugs such as pembrolizumab and nivolumab results in a robust antitumor immune response (14). Similarly, CTLA-4 inhibits the immune-stimulatory interaction between CD28 and B7-1 or B7-2 (24). Ipilimumab and tremilumab, mAbs to CTLA-4, thus prevent this immune-inhibitory process. The combination of ipilimumab and nivolumab could further enhance immune activation (18). However, in addition to the antitumoral immune activation, several undesired immune-mediated adverse
effects have been reported, including immune-mediated pneumonitis, colitis, hepatitis, and hypophysitis (25).

In addition to direct damaging effects on tumoral cells, conclusive evidence exists that radiotherapy induces an immunogenic cell death (26, 27). These effects are mediated by release of tumor antigens and expression of damage-associated molecular patterns, such as upregulation of Fas and ICAM-1, and exposure of calretinin on the cell surface (28, 29). Accordingly, it has been postulated that radiotherapy may work as an inducer for the immune system, driving cytotoxic T cell-mediated destruction of cancer cells, thus augmenting the effect of immune therapy (30, 31). Likewise, evidence supports a disruptive effect of radiation-induced immunologically mediated process in the tumor and surrounding brain tissue might be exacerbated (20). This observation may also explain the temporal relationship between the changes seen in the treated lesions in these two cases and initiation of immune therapy. Another important consideration is the characteristics of the histologic findings. Although the current report did not show significant histologic differences from our previously reported cases of post-SRS leukoencephalopathy (2, 4), it is possible that as more cases are identified in the future, potential subtle differences in histopathologic appearance after SRS with immunotherapy versus SRS alone will be identified.

Surgical management provided confirmation of diagnosis and rapid symptomatic relief and allowed both patients to

**Figure 4.**

A and B, representative H&E sections of the resected lesion following SRS showing predominant necrosis and minute collections of tumor cells (upper right; ×4 and ×10). C, CK7 immunostain highlights the small collection of tumoral cells (×10). D, a representative H&E section of the surrounding brain tissue depicting an intense vasculitic process characterized by hyalinization of vessel walls and infiltration by inflammatory cells (×20). E, CD3 immunostain highlights the T lymphocytes infiltrating the vessel wall (×20). F, CD68 immunostain highlights the macrophages and microglial cells infiltrating vessel walls and the surrounding brain tissue (×20).
resume systemic immunotherapy within several weeks. Awareness of the potential interaction between the effect of SRS and PD-1 mAbs is imperative to avoid the misinterpretation of radiologic changes as tumor progression, which could otherwise lead to inappropriate re-irradiation or cessation of an effective therapy and potentially harmful consequences (6). If this significant interaction between SRS and immunotherapy is confirmed at other centers, changes in management options such as first-line surgical management of brain metastases or lower-dose SRS may need to be considered in patients with brain metastases being offered immunotherapy.

Disclosure of Potential Conflicts of Interest
A. Chiang reports serving as a consultant/advisory board member for Genentech/Roche. S. Gettinger reports serving as a consultant/advisory board member for Bristol Myers-Squibb. S.B. Goldberg reports receiving commercial research support from AstraZeneca and Merck. H.M. Kluger reports receiving speakers bureau honoraria from Merck and Regeneron. No potential conflicts of interest were disclosed by the other authors.

References

486 Cancer Immunol Res; 4(6) June 2016 Cancer Immunology Research

Authors’ Contributions
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.K. Alomari, A.O. Vortmeyer, A. Chiang, S. Gettinger, V.L. Chiang
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.K. Alomari
Study supervision: S. Gettinger, V.L. Chiang

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