The central nervous system (CNS) is a common site of metastatic disease in NSCLC patients. Approximately 30% to 50% of these patients can develop CNS progression during the course of treatment. Cytotoxic chemotherapy and targeted drugs have been reported to have limited efficacy for the treatment of brain metastasis (BM) because of the blood brain barrier. Regarding the efficacy of anti–programmed cell death 1 (PD-1) inhibitors for treating BM, pembrolizumab was shown to have some activity against BM in patients with melanoma or NSCLC with an acceptable safety profile. This suggests that there might be a role for systemic immunotherapy in patients with untreated or progressive BMs. In addition, Hubbeling et al. recently reported that treatment with cranial radiotherapy (RT) and PD-1 pathway blockade did not exert RT-related toxicity. However, the data on the efficacy and safety of anti-PD-1 inhibitors remain limited because studies have been conducted in small numbers of patients with BM, and excluded patients with larger BM, pre-treated BM with radiotherapy (RT), patients with associated neurological symptoms, or patients undergoing corticosteroid treatment. Here we report a case of a patient who experienced hemiparesis immediately after initiation of nivolumab treatment due to the enlargement of his ring-enhancing lesion (observed by brain magnetic resonance image [MRI]) and perilesional edema around the BM site pretreated with stereotactic radiotherapy (SRT).

**Case Report**

The patient was a 62-year-old man who had previously received chemotherapy (carboplatin and pemetrexed) for advanced disease. After 6 courses of chemotherapy, he developed an isolated CNS metastasis in the left occipital lobe (Figs. 1A and B); this lesion was treated with SRT of 36 Gray in 4 Fractions (9 Gray in 1 fraction). Six months after treatment with SRT, the size of the CNS metastasis and perilesional edema were reduced, but his primary lesion progressed; therefore, nivolumab treatment was initiated (3 mg/kg every 2 weeks) (Figs. 1C, 1D, and 2A). Two weeks after the initiation of nivolumab, hemiparesis suddenly developed in the patient. Brain MRI showed enlargement of the ring-enhancing lesion and perilesional edema (Figs. 1E and F). The patient then started treatment with a corticosteroid (dexamethasone, 4 mg/d), and right-sided hemiparesis was partly improved. He then underwent resection of the solitary CNS lesion. Pathologic findings revealed that most of the resection area had scattered adenocarcinoma in a background of extensive necrosis (Fig. 3). On the other hand, computed tomographic scan showed a significant improvement of pulmonary lesion (Fig. 2B). Treatment with nivolumab was then resumed, and
the patient remained free of disease progression after 14 months on therapy.

Discussion

The present case report showed that anti-PD-1 inhibitor can lead to the enlargement of the ring-enhancing lesion and perilesional edema immediately after nivolumab treatment.

Preclinical studies have shown that the combination of RT and targeted PD-1/programmed death ligand 1 therapy activates cytotoxic T-cells, reduces myeloid-derived suppressor cells, and can induce a synergistic effect, which is related to the abscopal effect.3,4 Some case reports have revealed that combination therapy with local RT and immune checkpoint inhibitors synergistically induce antitumor effects.5,6 On the other hand, anti-PD-1 inhibitors have been reported to induce the radiation recall lasting up to 2 years post-radiotherapy, which leads to the usage of anti-inflammatory drugs such as steroids.7,8 The safety data regarding the use of RT in the context of anti-PD-1/programmed death

Figure 1. Brain magnetic resonance images before stereotactic radiotherapy (SRT). (A) T1-weighted (T1WI). (B) T2-weighted (T2WI). (C,D) Images 6 months after SRT (T1WI, C; and T2WI, D). (E,F) Images 2 weeks after the initiation of nivolumab treatment (T1WI, E; and T2WI, F).

Figure 2. Computed tomography of primary lung lesions before (A) and 2 months after (B) the initiation of nivolumab treatment.
ligand 1 therapy remains limited, particularly for brain metastasis patients pretreated with SRT.

For the case here reported, the possibility that pseudoprogression from radiation necrosis might have been responsible for the enlargement of the ring-enhancing lesion and perilesional edema cannot be ruled out. However, the size of the BM and perilesional edema around the SRS-pretreated metastasis site had improved. There had been no associated neurological symptoms and unstable BMs until the initial dose of nivolumab, but hemiparesis suddenly developed just after nivolumab treatment. The phenomenon in this case was not typical pseudoprogression from radiation necrosis. On the other hands, the pathologic findings of CNS lesions showed scattered residual tumors surrounded by extensive necrosis, which indicated a radiation necrosis resulting from SRS. Therefore, we believe that nivolumab could enhance the brain tissue’s inflammation in the irradiated field, and induce pseudoprogression from radiation necrosis resulting from SRS. In fact, Martin et al. recently reported that combining immunotherapy and SRT in patients with BM have higher radiation necrosis risk. However, the exact mechanism how anti–PD-1 inhibitors induces pseudoprogression from radiation necrosis resulting from SRS remains unclear, and further investigation about that is needed.

Finally, if patients experience progression of ring-enhancing lesions and perilesional edemas after administration of anti–PD-1 inhibitors, this can lead to serious neurologic and life-threatening complications, as skulls are enclosed in the intracranial space. Indeed, Kanai et al. recently reported that the most frequent cause of nivolumab treatment discontinuation in advanced NSCLC was neurologic exacerbation.

Accordingly, the patient described in the present case report discontinued nivolumab treatment due to hemiparesis. Therefore, treatment with SRT for larger BM lesions might be a risk factor for anti-PD-1 inhibitors induced pseudoprogression from radiation necrosis around pretreated BM sites. However, the details of this phenomenon remains to be determined. Further investigation of the efficacy and safety of combining immune checkpoint inhibitors for SRT-pretreated brain lesions, including the timing of radiotherapy, is warranted.

References

Figure 3. Resected brain nodule shows necrosis with a few clusters of cancer cells (A). With higher magnification, papillary growth of cancer cells indicates adenocarcinoma (B).