Radionecrosis mimicking pseudo-progression in a patient with lung cancer and brain metastasis following the combination of anti-PD-1 therapy and stereotactic radiosurgery: A case report

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Abstract. Brain metastases (BMs) usually develop in patients with non-small cell lung cancer. In addition to systemic therapy, radiation therapy and surgery, anti-programmed cell death-ligand 1 (PD-L1) therapy is another promising clinical anticancer treatment modality. However, the optimal timing and drug-drug interactions of anti-PD-L1 therapy with other combined treatments remain to be elucidated. Treatment with anti-PD-L1 therapy is associated with an increased risk of radionecrosis (RN) regardless of tumor histology. The present study described a case of RN in a patient with lung adeno-carcinoma and with BM who received anti-PD-L1 therapy. Before anti-PD-L1 treatment, the patient received whole brain radiotherapy. During durvalumab treatment, the intracranial metastases regressed. The progression of intracranial lesions 9 months later prompted a second-line of therapy with PD-L1 inhibitor durvalumab and stereotactic radiotherapy (SRT). Despite stereotactic irradiation, the lesions progressed further, leading to surgical resection. On examination, RN was detected, but there was no evidence of metastatic lung cancer. The aim of the present study was to present the longitudinal change in magnetic resonance imaging in RN following STR and anti-PD-L1 combined therapy. The atypical image of RN is conditionally important for making an accurate preoperative diagnosis.

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Introduction

Brain metastases (BMs) are the most common type of tumor in the central nervous system in adults, occurring in ~20% of malignant tumors (1). BMs are most common in patients with lung cancer compared with other types of cancer and lung cancer is responsible for ~50% of all BM cases worldwide, which poses a threat to the improvement and effectiveness of oncological treatment (2). In addition to traditional methods such as chemotherapy, radiation therapy, surgery and molecularly targeted therapy that have been used in the past, emerging immunotherapeutic agents, such as checkpoint inhibitors, are also demonstrating promising therapeutic results in the treatment of lung cancer BMs (3). The development of immune checkpoint inhibitor (ICI) therapy, such as anti-programmed cell death-ligand 1 (PD-L1) therapy, has been reported to be effective in numerous types of cancer, including non-small cell lung cancer and small cell lung cancer (4). In addition, ICI therapies have been evaluated in patients receiving combination therapy, especially radiotherapy. The results obtained from clinical trials provide evidence supporting the safety and efficacy of radiotherapy in combination with anti-PD-1/PD-L1 treatment, which could be more effective than monotherapy (5). Magnetic resonance imaging (MRI) is the most commonly used modality to investigate radionecrosis (RN) (6). However, the imaging features of RN and tumor recurrence overlap considerably, with both entities demonstrating a degree of contrast enhancement and perilesional edema (7,8). Accordingly, a range of clinical and imaging strategies are being developed to evaluate tumor responses and to rule out pseudo-progression or RN. An accurate differential diagnosis is required for decision-making in the management of patients.

Case report

A 61-year-old female patient with stage IV adenocarcinoma of the lung was initially admitted to Suning County People's Hospital (Cangzhou, China) with a 6-month history of a dull headache and left upper limb weakness in December 2020. In

Suning County People's Hospital, the patient ordered a service to perform next-generation sequencing (NGS) and PD-L1 immunohistochemistry (Topgen-Biopharm). The NGS was performed using an OncoDrug-Seq™ kit (Topgen-Biopharm) for a panel of 33 tumor-targeting genes and was performed on the NextSeq500 system (Illumina, Inc.). The lung cancer samples were fixed with 10% formalin at room temperature for 24 h and 4-μm paraffin-embedded samples were used for PD-L1 immunohistochemistry. Rabbit anti-human mono-clonal antibodies to PD-L1 (1:50; cat. no. ab205921; Abcam) were used. Briefly, sections were dewaxed, dehydrated with a series of alcohol (70, 80 and 95%) at room temperature (1 h for each alcohol concentration) and the tissues were then placed in toluene for 30 min at room temperature for deparaffiniza-tion. After neutralization of endogenous peroxidase with 3% H_2O_2 at room temperature for 15 min and microwave antigen retrieval (800 W in 0.01 M citrate buffer pH 6), slides were preincubated with 5% bovine serum albumin blocking buffer (Thermo Fisher Scientific, Inc.) for 1 h at room temperature and then incubated overnight with monoclonal antibodies at 4˚C. Subsequently, the sections were serially rinsed, incubated with Goat anti-Rabbit IgG H&L (HRP) secondary antibodies (1:200; cat. no. ab97051; Abcam) and avidin-biotinylated peroxidase complex for 1 h at 37˚C, and again washed for 10 min with PBS at 37˚C. Nuclear counterstaining was performed with DAPI (cat. no. C1005; Beyotime Institute of Biotechnology) at room temperature for 5 min. The immunohistochemistry images were obtained using a light microscope. The results of immunohistochemistry indicated PD-L1 positivity (Fig. 1).

Based on these results, the patient decided to undergo further clinical treatment at the Department of Oncology of the Affiliated Hospital of Hebei University (Hebei, China). An initial computed tomography scan in the Affiliated Hospital of Hebei University revealed that the patient presented with a space-occupying lesion in the superior lobe of the right lung, with multiple bilateral pulmonary nodules and with masses in the mediastinal lymph nodes and liver. Brain MRI revealed a space-occupying lesion in the frontal parietal lobe (Fig. 2A). The patient received single-agent paclitaxel therapy for 2 cycles (intravenously; 135 mg/m², 3 weeks per cycle). On routine reex-amination, MRI revealed an enlarged space-occupying lesion (Fig. 2B). The patient was then treated with direct tomotherapy (planning target volume, 36 Gy/3 Gy/12 fx). Bevacizumab (intravenously, 15 mg/kg) and paclitaxel (intravenously, 175 mg/m²)-carboplatin (intravenously, 5 mg) chemotherapy was used for 6 cycles (21 days per cycle), which demonstrated regression in BM (Fig. 2C). However, new extrapulmonary metastases in the pancreas, kidney and ovaries were detected. Based on the results of the PD-L1 immunohistochemistry, the PD-L1 inhibitor, durvalumab (intravenously, 20 mg/kg), and systemic chemotherapy (camrelizumab (intravenously, 20 mg) plus anlotinib (orally, 12 mg) and gemcitabine (intravenously, 1,000 mg/m²) for 3 cycles and duvaliumab (intravenously, 10 mg/kg) plus anlotinib (orally, 12 mg) and gemcitabine (intra-venously, 1,000 mg/m²) for 9 cycles (21 days per cycle) were administered to the patient (Fig. 2D). However, the progression of BM prompted stereotactic radiotherapy (SRT) with 12 Gy radiosurgical volume (Fig. 2E). Therapy with a combination of anlotinib (orally, 12 mg) and gemcitabine (intravenously, 1,000 mg/m²) was then administered to the patient for

11 cycles (21 days per cycle). Brain MRI revealed an abnormal signal (no enhancement) and intracranial nodular enlargement (Fig. 2F). After 13 cycles of treatment with anlotinib and gemcitabine, brain MRI demonstrated an enlarged nodule with strong enhancement (Fig. 2G and H). Before SRT, magnetic resonance spectroscopy (MRS) was performed. The results suggested pseudo-progression with choline/N-acetyl-aspartate ratio (Cho/NAA) 0.92, choline/creatine ratio (Cho/Cr) 1.95 and N-acetyl-aspartate/creatine ratio (NAA/Cr) 2.12. In the contra-lateral normal brain tissue, the metabolite ratios of Cho/NAA Cho/Cr and NAA/Cr were 0.672, 1.08 and 1.16, respectively. Three-dimensional arterial spin labeling (3DASL) of the brain revealed low perfusion in the intracranial nodule (Fig. 3A-C). Before the surgical operation, the patients had another MRS scan and the results suggested RN with Cho/NAA 1.54, Cho/Cr 1.79 and NAA/Cr 1.16. In the contralateral normal brain tissue, the metabolite ratios of Cho/NAA Cho/Cr and NAA/Cr were 0.537, 0.904 and 1.68, respectively. The 3DASL of the brain also revealed low perfusion in the intracranial nodule (Fig. 3D-F). The patient decided to undergo surgical treatment at the Department of Neurosurgery of the Affiliated Hospital of Hebei University. The progressive BM was surgically removed and subjected to neuropathological exami-nation. The brain tumor tissue was fixed with 10% buffered formalin at 37˚C for 8-10 min. Subsequently, sections (5 μm) were cut from paraffin blocks and stained with hematoxylin and eosin at room temperature for 5 min (cat. no. C0105M; Beyotime Institute of Biotechnology), and DAPI for histo-pathological examination under a light microscope (Leica DM4000 M; Leica Microsystems GmbH). Histopathological analysis revealed RN with no evidence of metastatic lung cancer (Fig. 4).

Discussion

The present case demonstrated the side effects of the concur-rent use of radiotherapy and anti-PD-L1 inhibitors in patients with BM. The principle of anti-programmed cell death protein 1 (PD-1)/PD-L1 therapy is to block the negative regulatory process of the PD-1/PD-L1 signaling pathway on T-cell acti-vation and proliferation by inhibiting the complex formed by PD-1 and its ligand, PD-L1. Thus, T cells gradually recover immune activity by reactivation of the recognition and necrotic function of tumor cells (9). PD-1/PD-L1 inhibitors combined with radiotherapy mediate the antitumor effect in the dynamic interaction between effector cells and regulatory cells, such as CD8-positive T cells and tumor-infiltrating Tregs (10). In a previous study, melanoma tumors were irradiated with 10 Gy radiation; after tumor radiation, two important co-stimulatory molecules, CD86 and CD70, were revealed to be substantially upregulated on dendritic cells, which serve an important role in T-cell-mediated immune responses (11). Radiotherapy can regulate the expression of immune checkpoints, affect the expression levels of cytokines and promote the antitumor effects of immune drugs. Evidence has shown that several inflammatory cytokines, including tumor necrosis factor α, interleukin 1 and interleukin 2 can be upregulated by radiation therapy, which may be caused by an acute-phase inflamma-tory response (12). Conversely, radiation therapy can lead to substantial increases in the immunosuppressive cytokine
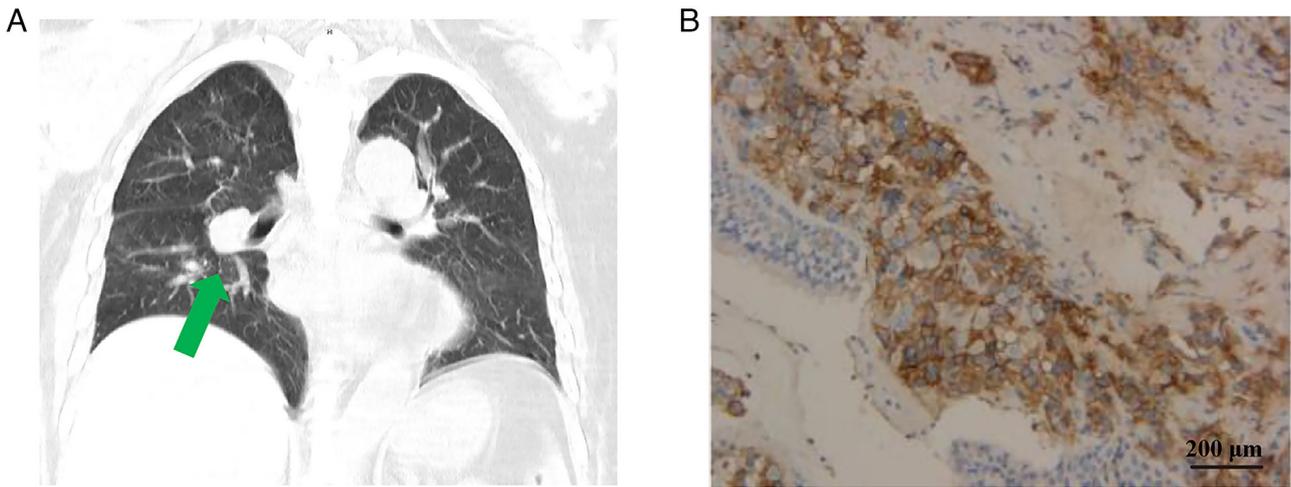
Figure 1. Immunological exanimation of PD-L1 of lung tissue. (A) A computed tomography image of the lungs of the patient. Arrow indicates the tumor. (B) PD-L1 immunological staining in lung cancer tissue. Scale bar, 200 μm. PD-L1, programmed cell death ligand 1.
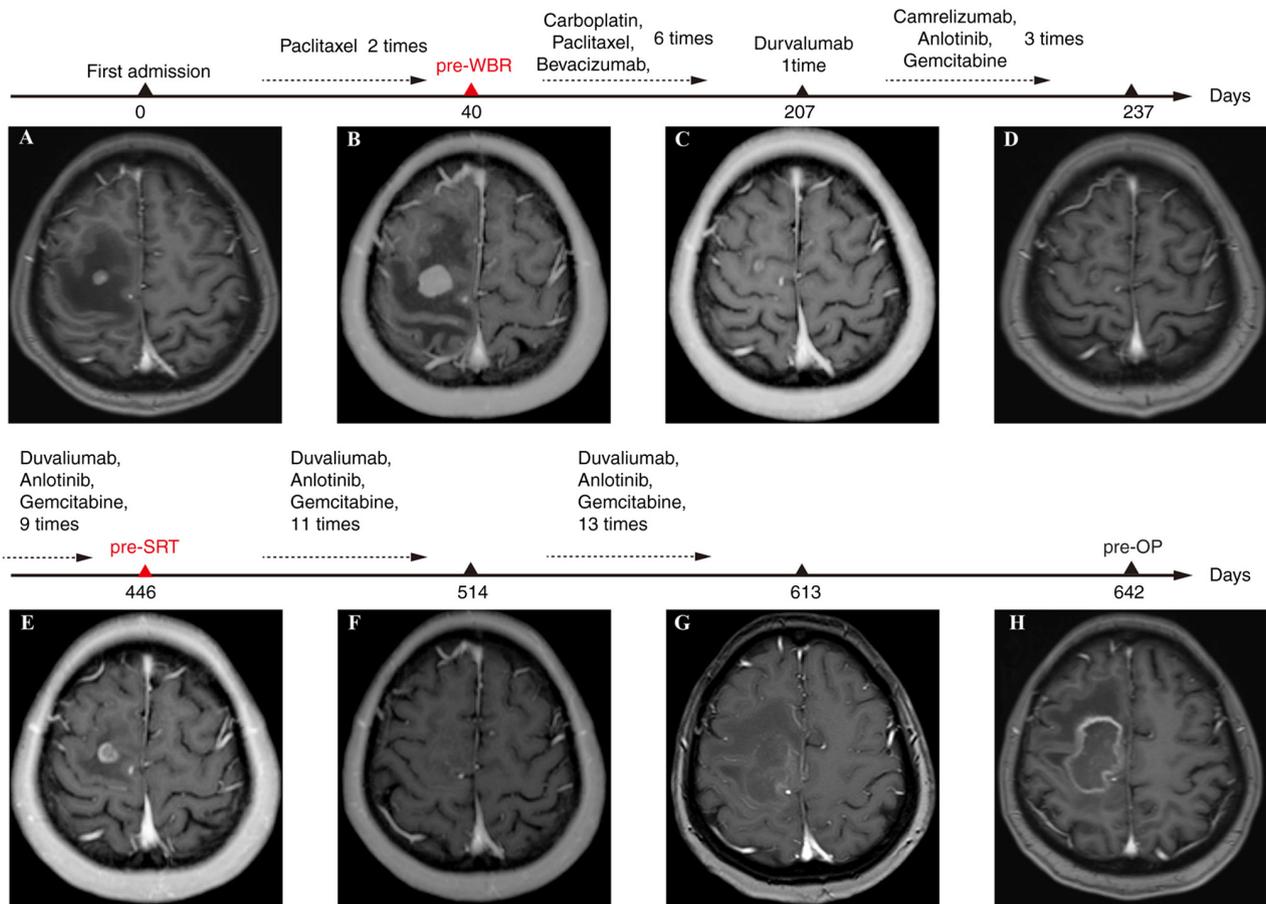

Figure 2. Timeline of the treatments and longitudinal enhanced MRI of intracranial lesions. (A) Enhanced MRI of right frontal metastasis at initial diagnosis. (B) Before receiving whole brain radiosurgery, the lesion was treated with paclitaxel. (C) Subsequently, the patient began bevacizumab and paclitaxel-carbo-platin chemotherapy for 3 cycles and durvalumab treatment for 1 cycle. (D) Enhanced MRI of right frontal metastasis following 3 cycles of treatment with camrelizumab, anlotinib and gemcitabine. Enhanced MRI of right frontal metastasis following (E) nine, (F) 11 and (G) 13 cycles of treatment with duvaliumab, anlotinib and gemcitabine. (H) Enhanced MRI of right frontal metastasis before surgery. MRI, magnetic resonance imaging; WBR, whole brain radiosurgery; SRT, stereotactic radiotherapy; pre-OP, pre-operation.

transforming growth factor β in in response to cell death and stress, which have important roles in dampening radia-tion-induced immune responses (13). Inflammatory cytokines released from the irradiated tissue and the upregulation of checkpoint ligands can prevent autoimmune responses against healthy and malignant cells. In one study, radiation-induced
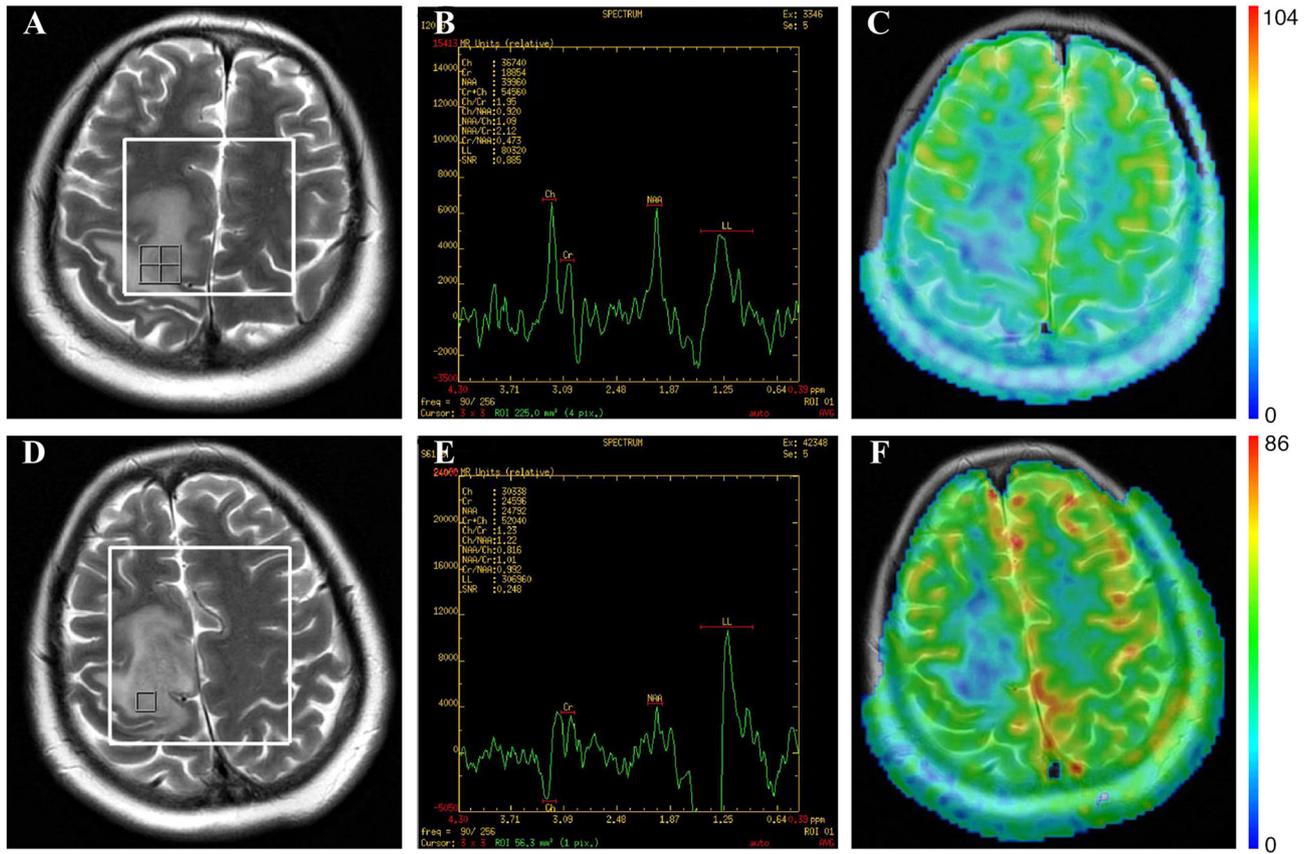
Figure 3. Preoperative MRS and 3DASL images of brain metastasis. (A) T2-MRI of intracranial nodules using Fig. 2G as a reference. (B) An MRS image of the intracranial nodules using Fig. 2G as a reference. (C) An 3DASL image of the intracranial nodules using Fig. 2G as a reference. (D) T2-MRI of intracranial nodules using Fig. 2H as a reference. (E) An MRS image of the intracranial nodules using Fig. 2H as a reference. (F) An 3DASL image of the intracranial nodules using Fig. 2H as a reference. (C and F) The color scale shows the expression level of metabolites. red represents high expression and blue represents low expression. MRS, magnetic resonance spectroscopy; 3DASL, three-dimensional arterial spin labeling; T2-MRI, transverse relaxation time-magnetic resonance imaging.

upregulation of PD-L1 on the surface of tumor cells was shown to be dependent on interferon γ derived from CD8 T cells (14). In contrast, PD-1/PD-L1 inhibitors can promote radiotherapeutic effects by inhibition of negative immune-regulatory cells or molecules (15-17). For example, a previous study have showed that PD-1/PD-L1 monoclonal antibody could restore T-cell activity, reduce Treg numbers and increase CD8+T/Treg ratio, thus enhancing tumor cell death (18). A case-control trial with 93 patients by Trommer *et al* (19) suggested that the use of PD-1 inhibitors combined with radiotherapy had benefits and could improve overall survival rates. However, with the wide application of combination therapy in clinical practice, an increasing number of studies have reported adverse reactions after the use of PD-1/PD-L1 inhibitors (20-22). A previous study indicated that anti-PD-1 therapy could increase the risk of RN when combined with radiotherapy (23). The present case highlights the difficulty in differentiating between RN and pseudo-progression, following sequential treatment with PD-1/PD-L1 inhibitors and radiotherapy.

In the present case, the patient also received bevacizumab. Bevacizumab, a recombinant human monoclonal antibody, binds vascular endothelial growth factor (VEGF) and prevents VEGF from binding its receptors (VEGFR-1 and kinase insert domain receptor) on the endothelial cell surface, which serves a role in pruning blood vessels, regulating vascular permeability, reducing brain edema caused by brain necrosis and treating brain necrosis (24). In 2007, Gonzalez *et al* (25) first reported using bevacizumab to treat radiation brain necrosis. At present, clinical studies have proven the clinical efficacy of bevacizumab. For example, Dashti *et al* (26) reported that a single low-dose targeted bevacizumab infusion resulted in durable clinical and imaging improvements in 80% of patients. Another randomized double-blind study with 14 patients also supported consideration of this treatment option for patients with RN (27). At present, the majority of patients respond well to bevacizumab. However, the effect of bevacizumab on RN could not be ruled out in the present case. Jeyaretna *et al* (28) reported an exacerbation of cerebral RN by bevacizumab, which could lead to the hypothesis that initial treatment with bevacizumab might result in a reduction in cerebral edema. However, prolonged treatment might result in the over-pruning of at-risk blood vessels within the radiation field. The underlying mechanisms of bevacizumab-induced enlargement of RN remains unclear. At present, the duration, optimal dose and dosing interval of bevacizumab, require further evaluation.

A previous study has reported that the incidence of radiation-induced brain necrosis in patients with melanoma brain metastasis treated with SRT combined with PD-L1 immunotherapy was increased in a retrospective analysis of
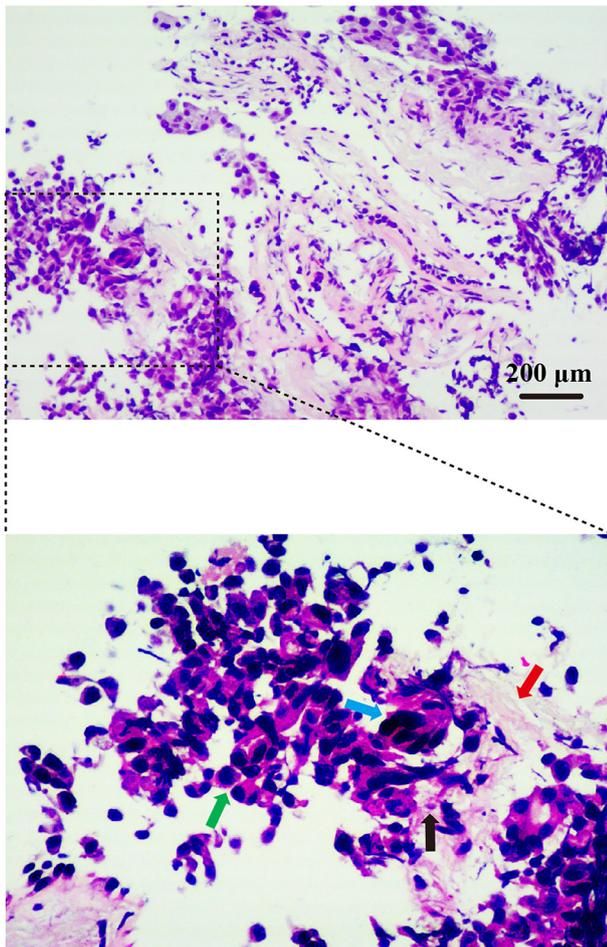
Figure 4. Histological analysis of the resected lesion. H&E staining of the specimens indicated necrosis (red arrow), hypercellularity with scattered foamy macrophages (green arrow), reactive astrocytes (black arrow) and rare atypical cells (blue arrow). Upper panel: Scale bar, 200 μm; lower panel: 4x magnification.

patients with melanoma treated with SRT (29). The study by Pires da Silva *et al* (30) followed-up 135 patients with melanoma that received radiotherapy combined with PD-L1 immunotherapy for an average of 23.6 months and revealed reported the probability of RN was 17% along with a cumulative incidence rate of 18% in 2 years. Furthermore, it was proposed that the time of occurrence of RN-associated symptoms was similar to the time of occurrence of radiological abnormalities (30). It has been previously reported that the rate of RN was increased with the addition of concurrent systemic therapies to SRT and whole brain radiotherapy (WBRT) (Table I) (30-35). A corresponding increase in RN was not reported in patients treated with concurrent therapies and SRT alone. The present case is consistent with the findings of a previous study (30), suggesting that anti-PD-1 therapy may increase the risk of RN when combined with radiotherapy. In the present case, the patient received the PD-L1 inhibitor duvaliumab and SRT. Approximately 3 months following the combined therapy, the brain MRI indicated an abnormal signal (no enhancement), and ~7 months later, the intracranial nodule was enlarged. MRS suggested RN. The 3DASL of the brain also indicated low perfusion in the intracranial nodule. Pathological examination also indicated RN. Numerous previous studies have reported

that SRT combined with immunotherapy increased the risk of radiation necrosis (31,36,37). Therefore, the concern regarding the potential risk of RN following SRT combined with PD-L1 immunotherapy has increased. Numerous previous studies have reported that PD-L1 immunotherapy combined with brain radiotherapy is effective and feasible. However, due to the potential of adverse reactions, the sequence, dosage and volume should be strictly controlled during the combined treatment, and imaging should be closely monitored to reduce the occurrence of adverse reactions such as RN. In the present case, it was demonstrated that the size of the intracranial nodules gradually decreased. After SRT, brain MRI indicated an abnormal signal (without enhancement), and that the intracranial nodule was enlarged. At this stage, it was not easy to differentially diagnose RN from tumor recurrence because of their shared clinical symptoms such as symptoms of increased intracranial pressure and/or seizures, and conventional imaging and pathological biopsy are still the best methods for differential diagnosis. However, it is difficult to perform surgery in the early clinical stage. Therefore, dynamic MRI sequence monitoring is often used to confirm the diagnosis in the clinic. In the early stages, traditional imaging of RN and tumor progression may demonstrate contrast enhancement on MRI, and large edema zones are usually observed around the lesions. In the long-term follow-up, RN indicated a decrease in tumor volume, while tumor progression indicated an increase in tumor volume (38-40). In these patients, the T2-weighted image margin 'mismatched' the contrast-enhanced T1-weighted image margin. When the lesion appears indistinct on T2, the histology usually indicated necrosis and contrast enhancement when the contrast-enhanced rim on the T1-weighted image is associated with a distinct border on T2, and the pathology was usually a recurrent tumor (39). MRI findings of RN are often described as 'Swiss cheese' or 'soap bubble' lesions (40). At present, RN, tumor pseudo-progression and tumor recurrence have different treatment strategies. Pseudo-progression is defined as a radiographic increase in enhancement and/or edema on MRI without tumor progression. This transient increase in enhancement and/or edema exhibits spontaneous recovery, which usually occurs within a few weeks or months after the onset of pseudo-progression (41). Tumor recurrence may require surgical intervention. For RN, therapy involves corticosteroids, bevacizumab or surgical intervention (42). It is difficult to distinguish between RN, tumor pseudo-progression and tumor recurrence using conventional structural MRI at an early stage. Currently, regional cerebral blood volume and amino acid positron emission computed tomography (PET) are used to differentiate the diagnosis of these conditions. The most common imaging marker of RN in conventional MRI is the 'Swiss cheese' pattern with diffuse enhancements at the margins between the cortex and white matter (43). In the present case, these features were not apparent on enhanced MRI. Therefore, it was suspected that the local tumor had recurred. However, bevacizumab treatment might influence the results of MRS. Pseudo-progression usually occurs 2-5 months after radiotherapy, is self-limiting and curable. Post-radiation damage occurs after a delay of >6 months from the time of radiation and consists principally of necrosis caused by blood-brain barrier (BBB) disruption and radiation-induced demyelination leading to white matter

Table I. Reported rates of radiation necrosis with anti-PD-1 therapy combined with radiation therapy.

First author, year	Histology	Cases, n	Systemic treatment	Radiation necrosis rate (%)	(Refs.)
Pires da Silva *et al*, 2019	Melanoma	137	Anti-CTLA4, anti-PD-1 and all patients received immunotherapy combined with radiotherapy	27	(30)
Kim *et al*, 2017	Melanoma	135	Radiotherapy and anti-PD-1 therapy	17	(31)
Colaco *et al*, 2016	Melanoma, lung, breast, renal and colorectal cancer	42/180 received immunotherapy	Anti-CTLA4, anti-PD-1 and all patients received immunotherapy combined with radiotherapy	37.5 with immunotherapy only	(32)
Martin *et al*, 2018	Melanoma and lung cancer	115	Immune checkpoint inhibitors therapy combined with radiotherapy	20	(33)
Weingarten *et al*, 2019	Melanoma, renal-cell carcinoma, lung and breast cancer	57	Immunotherapy combined with radiotherapy	7	(34)
Andring *et al*, 2023	Melanoma and lung cancer	63	Anti-CTLA4, anti-PD-1 and radiotherapy	22	(35)

CTLA4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1.

injury (44). RN involves a space-occupying necrotic lesion with a mass effect and neurological dysfunction (45). It is not a self-limiting disease and therefore requires specialized treatment (46).

Generally, MRS could not be used to obtain an affirmative conclusion to diagnose 'pseudo-progression' or 'RN'. One of the main challenges for neurosurgeons or treating clinicians is to make a differential diagnosis of either tumor recurrence, RN or pseudo-progression in clinical settings. Even with improving neuroimaging methods or different diagnostic imaging modalities, such as diffusion-weighted imaging/diffusion tensor imaging, MRS and PET/single photon emission computed tomography, it is still challenging (47). MRS is a metabolic imaging technique that could provide value in differentiating pseudo-progression from recurrent tumors by identifying specific metabolites within the tumor that are present during active tumor growth (48). Previous studies have reported increased total choline levels in recurrent disease and reduced choline levels in tumors which exhibited pseudo-progression (49,50). Tumor recurrence has been reported to show higher Cho/Cr and Cho/NAA values compared with those of RN (51,52). In the present case, bevacizumab treatment might have influenced the results of MRS. Previous studies have reported that bevacizumab treatment could impact tumor energy and membrane metabolism, which resulted in increased intracellular pH and a decrease in the ratio of phosphatidylcholine to glycerophosphocholine

or Cho/NAA values (53,54). However, in the present study, this finding was confirmed using histological examination. In the present case, there was a longitudinal change in the MRI of RN following SRT and anti-PD-L1 combined therapy. Dynamic changes in RN on enhanced MRI was demonstrated. By employing longitudinal MRI, the present case revealed atypical images of RN. These treatment-associated imaging changes were necessary for clinicians to make an accurate preoperative diagnosis in this case.

However, the exact molecular mechanism of SRT-induced RN is still unclear and has not been fully elucidated. Evidence has indicated that high-dose SRT can damage the vascular endothelium by destroying the BBB on a large scale, leading to intracranial vasogenic edema and then further to ischemia of the surrounding brain tissue (55). Furthermore, this leads to an increase in the levels of hypoxia inducible factor-1A and VEGF and finally leads to infarction and necrosis of the brain parenchyma. A previous study indicated that RN is associated with abnormalities in vascular structures, including telangiectasia, hyaline thickening of vessels and fibrinoid necrosis with intravascular thromboses (56). The expression of VEGF promotes these abnormalities in newly formed vascular structures, increases the brittleness and permeability of vascular structures, and increases edema around the lesion (57). Certain scholars have proposed that radiation damage occurs through the combination of demyelination and vascular abnormalities (35,58). In the

penumbra around the necrotic nucleus, astrocytes, microglia and oligodendrocytes produce factors (e.g. VEGF) that promote cytokine release and increase the permeability of the BBB (37). However, the mechanisms by which the combination of anti-PD-L1 and radiotherapy promotes RN are still unclear. The main limitation of the present case report is that the patient received multiple different agents. As well as radiotherapy and anti-PD-1 therapy, the patient also received chemotherapy; therefore, the role of chemotherapy in the formation of RN could not be ruled out. The effect of bevacizumab on RN is uncertain. In the present case, it was hypothesized that neurological symptoms and radiologically suspected radioactive brain necrosis and tumor progression may occur after 7 months of treatment with a PD-L1 inhibitor and 2 months of treatment with SRT. The side effects of WBRT in the early stage are uncertain, and, to the best of our knowledge, there is not any literature which clearly reports that the simultaneous application of anlotinib and gemcitabine can increase the probability of radioactive brain necrosis.

In conclusion, the present study reported a case of RN following sequential PD-1/PD-L1-directed immunotherapy, WBRT and SRT. RN mimicked cancer progression with enlarged intracranial nodules. For the first time, the present study demonstrated the dynamic changes in RN on enhanced MRI.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XJ, LW, YT, YS, RH, CF, CL and LZ participated in the conception, design and data acquisition for the paper. XJ and LW participated in drafting and revising the manuscript. LZ critically revised the paper. LW ensured that questions related to the integrity of any part of the work were appropriately investigated and resolved. YT, YS, RH and CF confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of anonymized data and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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