

Ischemic Stroke with Multiple Cerebral Artery Stenosis in a Patient with an Anaplastic Astrocytoma during Bevacizumab Treatment: A Case Report

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Abstract

It has been reported that bevacizumab, an agent administered as an adjuvant therapy for high-grade gliomas, causes thromboembolic complications. We report a cerebral infarction with newly developed cerebral artery stenosis occurring during treatment with bevacizumab for an anaplastic astrocytoma. A 48-year-old female underwent excision surgery for an anaplastic astrocytoma on the right temporal lobe and received radiation therapy and chemotherapy with temozolomide. Twenty months after the maintenance therapy, treatment with bevacizumab was introduced for tumor recurrence. After the 14th course of bevacizumab at 6 months, 27 months after radiation therapy, the patient began experiencing mild right hemiparesis. Magnetic resonance imaging revealed scattered cerebral infarcts on the left frontal lobe and diffuse cerebral artery stenosis of the bilateral internal carotid artery system both inside and outside the radiation-treated area. Antiplatelet medication was commenced, and there was no recurrence of ischemic stroke. The morphological transition of the cerebral arteries should be carefully monitored *via* magnetic resonance angiography during post-radiation treatment with bevacizumab.

Keywords: stroke, cerebral ischemia, bevacizumab, glioma, radiation

Introduction

Bevacizumab (BEV), a monoclonal antibody to the vascular endothelial growth factor (VEGF), is administered as an adjuvant therapy for glioblastomas and other high-grade gliomas. While arterial thromboembolism has been identified as an adverse event that is triggered by BEV, detailed reports on its occurrence in glioma patients have been extremely scarce. Here we report a case of cerebral ischemic stroke in a patient with an anaplastic astrocytoma (AA).

Case Report

A 48-year-old female presented with a partial seizure of

the left face. She had no history of hypertension, diabetes mellitus, dyslipidemia, smoking, or other notable underlying diseases. Magnetic resonance imaging (MRI) revealed a tumorous lesion mainly located on the right medial temporal lobe. The lesion appeared with an iso-intensity signal on T1-weighted imaging and a high-intensity signal on T2-weighted imaging, with perifocal edema on fluid-attenuated inversion recovery (FLAIR) imaging and no Gadolinium (Gd) enhancement (Fig. 1A-D). Magnetic resonance angiography (MRA) revealed no stenosis or atherosclerosis of the cerebral arteries (Fig. 1E). Total tumor resection *via* craniotomy was performed, with no perioperative complications or neurological deficits. The histopathological examination revealed a proliferation of astrocytes with nuclear atypia without endothelial proliferation

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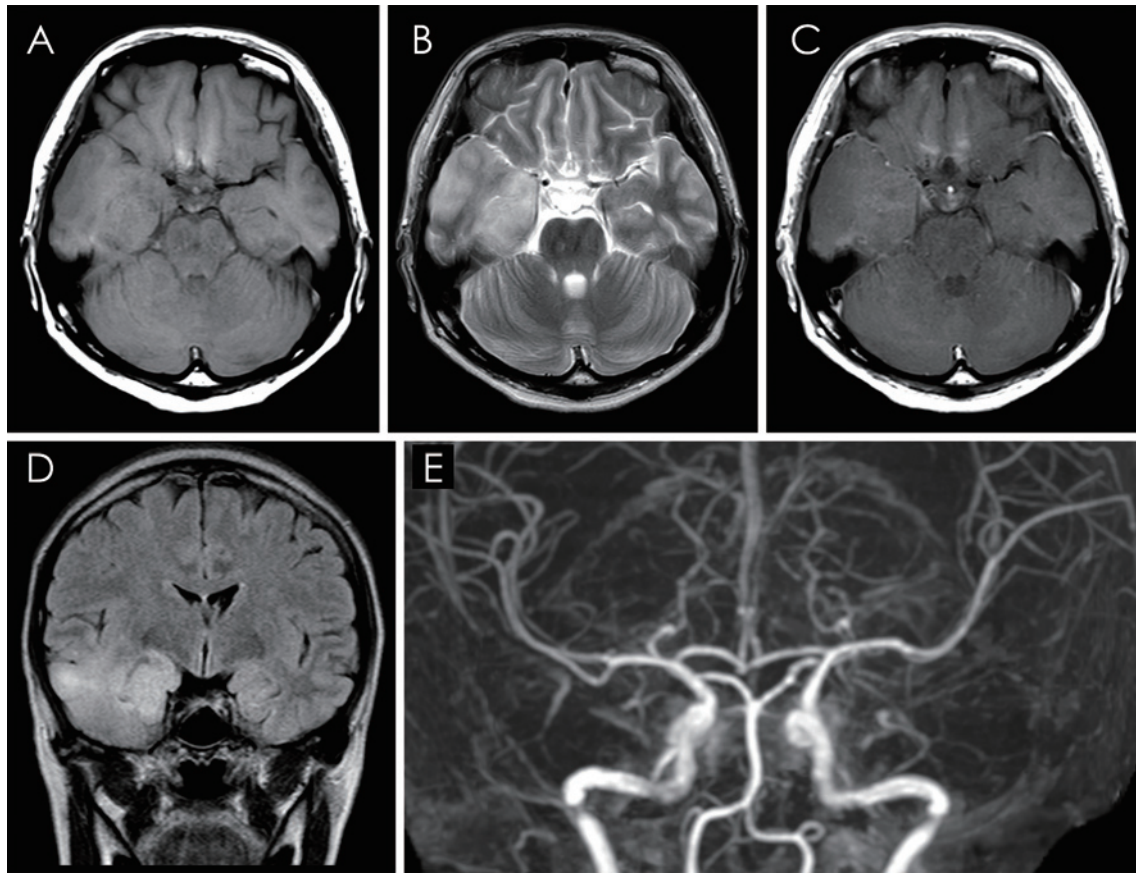


Fig. 1 Preoperative MRI image shows a tumorous lesion on the right medial temporal lobe. (A, T1-weighted imaging; B, T2-weighted imaging; C, T1-weighted imaging with contrast; D, Coronal FLAIR imaging.) MRA reveals no stenosis or atherosclerosis of the cerebral arteries (E).

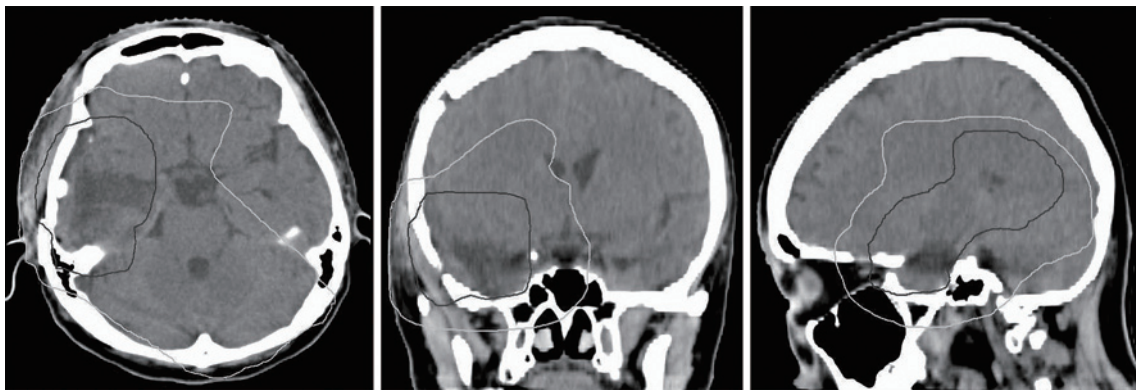


Fig. 2 Dosimetry maps of the radiation therapy with 59.4-Gy tumor dose. The inner enclosed area (black enclosing line) represents 98% of the radiation dose, and the outer enclosed area (white enclosing line) represents 50% of the radiation dose. Irradiation doses for contralateral MCA and ICA are calculated to be less than 28 Gy at maximum. Doses for the contralateral ACA are calculated to be less than 35 Gy at maximum. Doses for the bilateral ICAs of carotid portion are calculated to be less than 5 Gy.

or necrosis. The pathological diagnosis was AA (WHO grade III). Upon confirmation of the pathological diagnosis, the patient was started on radiation therapy with a 59.4-Gy tumor dose in 33 fractions and chemotherapy with temozolomide (TMZ) (Fig. 2).

After 20 months of maintenance chemotherapy with

TMZ, tumor recurrence on the bilateral ventromedial frontal lobe was detected on MRI and ^{11}C -methionine positron emission tomography (PET) (Fig. 3). The patient was started on a 10-mg/kg dose of BEV at 2-week intervals, in addition to the TMZ. After the 14th course of BEV at 6 months, 27 months after radiation therapy, the patient

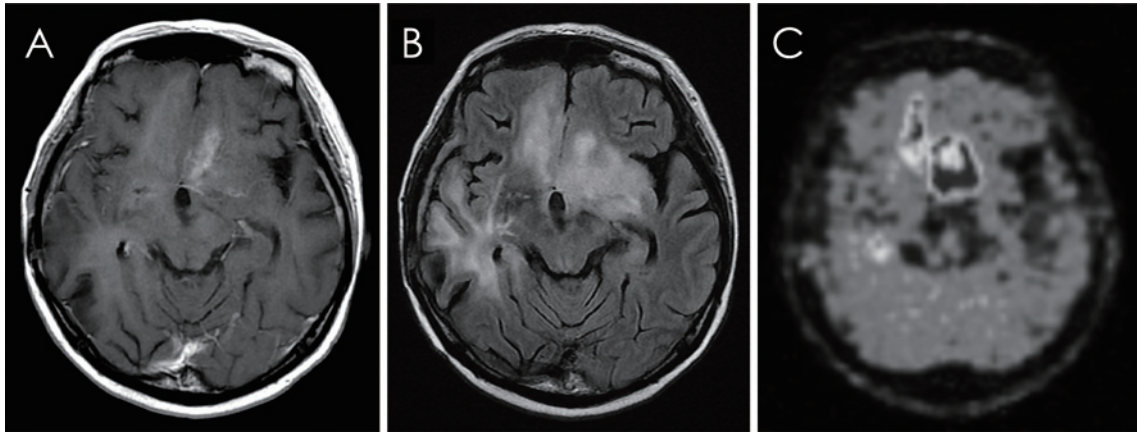


Fig. 3 (A, B) MRI reveals a new Gd-enhanced lesion on the left ventromedial frontal lobe and high-intensity signals on FLAIR imaging. (C) ^{11}C -methionine PET shows increased methionine uptake on the lesions.

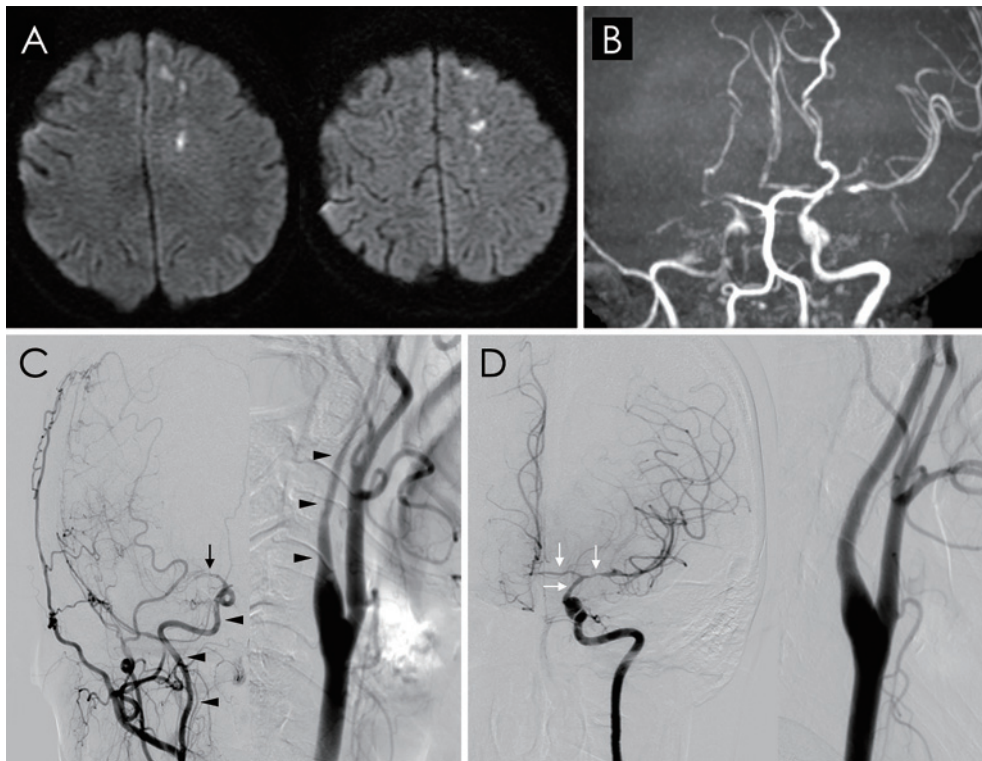


Fig. 4 (A) DWI shows scattered high intensity on the left frontal lobe. (B) MRA shows diffuse and severe cerebral artery stenosis. (C, D) The right and left CAG (anteroposterior view of the intracranial portion and lateral view of the carotid portion). The right ICA is severely stenosed from the carotid portion (black arrowheads) and occluded at the proximal portion of the MCA (black arrow). The left ICA is also stenosed, and severe stenosis is observed on the ACA and MCA (white arrows).

presented to our institution with subacute progression of mildly decreased reactivity and difficulty in handling her right hand. MRI showed cerebral infarcts scattered on the left frontal lobe on diffusion-weighted imaging (DWI) (Fig. 4A). In addition, MRA revealed diffuse cerebral artery stenosis of the bilateral internal carotid artery (ICA) system (Fig. 4B). No arterial stenosis had appeared on MRA when the brain tumor was diagnosed two and a half years

earlier. Digital subtraction angiography precisely confirmed the diffuse stenosis of the arteries (Fig. 4C and D). The right carotid angiography (CAG) revealed diffuse stenosis of the intracranial ICA and occlusion at the proximal portion of the middle cerebral artery (MCA), with no appearance of the anterior cerebral artery (ACA). The left CAG revealed stenosis of the intracranial ICA similar to that on the contralateral side, and stenosis of both the left ACA

and MCA was confirmed. In addition, stenosis of the ICA was observed at the carotid portion, especially on the right side. These findings were more severe in the areas exposed to high radiation doses but were also observed outside the target volume of the radiotherapy, such as the MCA on the contralateral side and the carotid portion (Fig. 2). Blood examinations revealed no abnormalities, including specific autoantibodies associated with vasculitis. There was no mutation in the RNF213 gene, which is associated with moyamoya disease and other intracranial artery stenosis.¹⁾ The BEV was discontinued, and antiplatelet therapy was commenced. The patient's activities of daily living gradually declined due to tumor progression, and she died after 5 months of palliative care without recurrence of ischemic stroke.

Discussion

BEV inhibits angiogenesis in cancerous cells and impedes tumor growth by suppressing VEGF as a monoclonal antibody.²⁾ BEV has been widely used in treating various malignant tumors, including colorectal cancer, non-small cell lung cancer, ovarian cancer, breast cancer, and high-grade glioma. Some adverse events of the agent have been identified, for example, wound-healing complication, gastrointestinal perforation, bleeding, venous thromboembolism, and cerebral ischemia.³⁻⁵⁾ Among cancer patients treated with BEV, the incidence of cerebral ischemia is slightly higher in patients with gliomas (1.5%-8.5%)⁶⁻⁹⁾ than in patients with colorectal cancers (0.3%-1.3%),¹⁰⁻¹²⁾ ovarian cancers (0.7%),¹³⁾ breast cancers (0.2%-1.9%),^{14,15)} prostate cancers (1%),¹⁶⁾ or renal cell carcinomas (1%).¹⁷⁾ The mechanism of arterial thromboembolism associated with BEV might be explained by the inhibition of VEGF, a process that suppresses antiproliferative effects in smooth muscle cells, antiplatelet actions, and vasodilation by reducing the endothelial production of nitric oxide and prostacyclin.^{18,19)} Although it has been reported that several types of cerebral infarction, such as large-vessel, cardioembolic, and lacunar, were observed in patients treated with BEV,⁶⁾ detailed reports on individual clinical courses have been extremely scarce,^{20,21)} and the mechanism of ischemic stroke and the morphological alteration of the arteries are unknown.

Before commencing BEV treatment, the present case underwent radiotherapy of the head, a known risk factor for atherosclerosis and subsequent ischemic stroke.^{22,23)} With regard to the radiation dose, it has been reported to cause atherosclerotic change of arteries at doses greater than 35 Gy.²³⁾ In the present case, stenosis was observed in contralateral MCA and ICA with a radiation dose of less than 28 Gy, suggesting that the pathophysiology of diffuse arterial stenosis could not be fully explained only by the effects of radiation. The combination of BEV medication and irradiation may increase the risk of ischemic stroke in glioma pa-

tients, who have a higher rate of thromboembolic complications than those with other cancers.

Another concern is the time passed between the initial BEV administration and the occurrence of cerebral ischemia. The period leading up to the cerebral ischemia is generally longer than the periods reported for other adverse events,⁶⁾ and the incidence of arterial stenosis is related to the time passed from the commencement of radiation therapy.²²⁾ For this reason, the incidence of cerebral ischemia will increase as patients with high-grade gliomas survive for longer periods. We should evaluate not only tumor recurrence *via* MRI but also morphological changes in the cerebral arteries *via* MRA. If stenotic changes are identified, the discontinuation of BEV and the introduction of antiplatelet therapy may result in overall benefits for activities of daily living.

Conclusion

We presented a case of ischemic stroke with newly developed diffuse and severe cerebral artery stenosis occurring during the treatment with BEV for an AA. The administration of BEV following radiation therapy may increase the risk of arterial thromboembolic complications. We considered that the morphological transition of the cerebral arteries should be regularly observed using MRA.

Conflicts of Interest Disclosure

None of the authors have conflicts of interest to declare.

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