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CASE REPORT PEER REVIEWED | OPEN ACCESS

A case of perforator area infarction during maintenance chemotherapy for insular glioma with bevacizumab

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ABSTRACT

Introduction: Glioblastoma multiforme is one of the most malignant central nervous system neoplasms. Maintaining good daily living activities during the tumor progression-free survival period is desirable. Neurological dysfunctions resulting from surgical treatment-related deficiencies or ischemic stroke during the established treatment protocol should be avoided.

Case Report: A 66-year-old woman was diagnosed with glioblastoma multiforme in the right insula. She underwent chemotherapy and radiotherapy following surgical resection. Following the initial standard treatment, she received maintenance chemotherapy, which included the administration of the antiangiogenic agent bevacizumab. During this period, she experienced a cerebral infarction with severe hemiplegia. Sixteen administrations of the antiangiogenic agent later, the perforator of the right middle cerebral artery became infarcted.

Conclusion: Antiangiogenic agents are known to cause vascular infarction complications. However, small vessel occlusion is rarely observed with this type of therapy. Previous reports on complications involving small vessel infarction show that adverse events typically occur several days after treatment, with one exception. This case demonstrates the rare occurrence of cerebral infarction shortly after treatment with an antiangiogenic agent.

Keywords: Bevacizumab, Cerebral infarction, Complication, Glioma

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INTRODUCTION

Glioblastoma multiforme (GBM) accounts for 14.5% of primary brain tumors [1]. Following standard treatment involving surgical resection, radiation therapy, and chemotherapy, the median overall survival rate is 15–18 months [2–4]. Glioblastoma multiforme is a malignancy with a poor prognosis and a 5-year survival rate of 7.2–16% [1, 4]. The median progression-free survival is 12 months [2, 5]. Maintaining an adequate level of activity of daily living (ADL) during the tumor-free period is desirable.

One case of GBM showed a declined ADL level due to complications from a stroke during maintenance chemotherapy. This report presents the case history alongside a literature review.

CASE REPORT

A 66-year-old woman came to the clinic complaining of cognitive dysfunction and left upper limb paraplegia. Head magnetic resonance imaging (MRI) revealed a mass lesion on the right insula (Figure 1A). The mass lesion showed hypo-intensity on the T1-weighted image (data not shown) and hyper-intensity on the T2-weighted image (data not shown), fluid-attenuated inversion recovery (FLAIR) image (Figure 1A), and diffusion-weighted image (DWI) (data not shown) in an MRI scan. A gadolinium contrast T1-weighted MRI image showed ring-like enhancement (Figure 1B). Positron emission

tomography (PET) imaging showed hyperaccumulation of fluorodeoxyglucose (FDG) and methionine (Figure 1C) in the lesion. These image findings were obtained within one week after the first diagnosis. Based on these imaging findings, a high-grade glioma was suspected. A right frontotemporal craniotomy was performed under general anesthesia to remove the tumor. Intraoperative microscopic examination revealed that the tumor tissue fluoresced due to metabolized substances from ingested 5-aminolevulinic acid (5-ALA). Pathological examination revealed atypical and polymorphous histology with vascular hyperplasia and necrosis. Immunohistochemical analysis revealed positive staining for glial fibrillary acidic protein (GFAP), oligodendrocyte transcription factor 2 (Olig2), and p53, as well as negative staining for isocitrate dehydrogenase 1 (IDH1) R132H exchange and positive staining for Ki67 LI at 15–20%. The presence of GFAP and Olig2 indicates that the tumor is derived from the glial lineage. The IDH1 R132H mutation is intact, and the histological features, including necrotic lesions and microvascular proliferation, confirm that the diffuse adult glioma is a GBM, which is classified as World Health Organization grade IV. The patient was diagnosed with GBM, isocitrate dehydrogenase-wild type (IDH-WT). Her intracranial lesion was sub-totally resected surgically. The tumor, located in the motor neuron area deep within the insular region, was left intact to preserve motor function. The remaining tumor was treated with a protocol that included temozolomide administration at a dose of 75 mg/m² for 42 days and 60 gray of radiation in 30 fractions of stereotactic radiotherapy (SRT) using TomoTherapy (Accuracy Inc., Madison, WI, USA), based on the Stupp regimen [2, 6]. She then continued maintenance chemotherapy with bevacizumab (10 mg/kg intravenously every two weeks) and temozolomide (150 mg/m² orally for five days every 28 days) for the residual lesion near the insula observed by gadolinium-contrasted T1 image of MRI (Figure 1D). She returned to her home life with only the neurological sequela of incomplete left paralysis (MMT 4/5). She achieved a functional recovery of two points on the modified Rankin Scale (mRS). The tumor mass and surrounding edema had almost disappeared in the FLAIR image of MRI (Figure 1E), which was obtained at the prior to the 16th administration of bevacizumab. Shortly after the 16th administration of bevacizumab, the patient undergoing maintenance chemotherapy developed left paralysis (MMT 1/5). A DWI of MRI of the head revealed a cerebral infarction complication in the right internal capsule to corona radiata (Figure 1F). The infarction was from a perforating branch of the right middle cerebral artery, but the main trunk vessel was not occluded (data of MR angiography is not shown). This adverse event occurred 10 months after the onset of GBM.

In summarized the clinical time course. She was treated the surgical operation at the day 12 post first diagnosis. Following the combined treatment according to the Stupp regimen was started at the day 26 post first diagnosis, which means post operation day 14. Maintenance chemotherapy with bevacizumab and temozolomide was started at the day 97 post first diagnosis, which means the 31 days after the Stupp regimen therapy finished. Cerebral infarction of right basal ganglia occurred at the 301 days post first diagnosis, which means the sixteenth bevacizumab time.

Following the stroke, maintenance chemotherapy, including bevacizumab, was discontinued. She also received rehabilitation and intravenous drip of extracellular fluid to prevent cerebral ischemic lesion expansion. However, due to the cerebral infarction, she suffered a residual left upper and lower extremity paralysis (MMT 2/5). Her ADL decreased to mRS 4.

The patient was transferred to the hospital for continued rehabilitation.

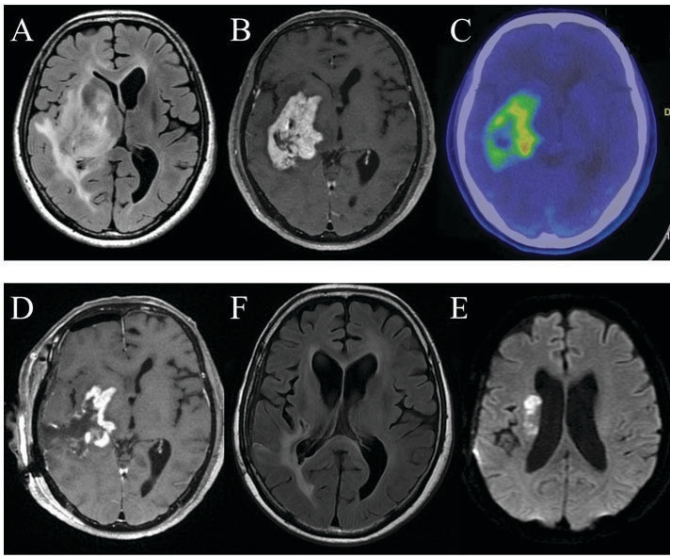

Figure 1: (A) The head magnetic resonance imaging (MRI) with fluid-attenuated inversion recovery (FLAIR) at the time of admission. (B) The gadolinium-enhanced T1-weighted MRI image at the time of admission. (C) A methionine accumulation image obtained via positron emission tomography (PET). (D) The gadolinium-enhanced T1-weighted MRI image after surgery. (E) The FLAIR image prior to the 16th bevacizumab treatment. (F) The diffusion-weighted image when the ischemic stroke occurred.

DISCUSSION

Bevacizumab is an anti-tumor drug indicated for treating solid tumors by inhibiting angiogenesis, its primary mechanism of action. This molecular-targeted drug directly binds to and inhibits the biological activity of vascular endothelial growth factor (VEGF), which regulates angiogenesis [7]. Bevacizumab is considered effective against GBM and other intracranial tumors [8–11]. However, the risk of thrombotic complications has been noted. In the international phase III clinical trial AVAglio (BO21990), thrombotic microangiopathy complications were observed in one of 464 patients (0.2%) with a first-episode GBM [11].

Various complications associated with cerebral infarction and bevacizumab administration have been reported [12–14]. Three cases of lacunar infarction associated with GBM treatment and one case associated with atypical astrocytoma were reported by Fraun et al. [15]. However, one of the cases associated with GBM occurred 16 months after the last bevacizumab dose, while the other occurred six months after the last dose. In contrast, three cases of cerebral infarction occurred within one week of the last bevacizumab administration [16–18]. A similar case involving the antiangiogenic agent aflibercept has also been reported. Four patients with cerebral infarction within a week of aflibercept administration have been reported [19–21]. Aflibercept is a VEGF competitive inhibitor and a fusion glycoprotein of VEGF. Of these cases, only one occurred eight hours after administration [21]. The direct causal role of bevacizumab administration in cerebral infarction development is unclear. However, bevacizumab is known to have vascular complication potentials including endothelial dysfunction due to VEGF suppression, prothrombotic states, microvascular collapse, impaired angiogenesis in irradiated fields, and disruption of autoregulation in microvascular system. These biological activities presumed to contribute the cerebral infarction in the basal ganglia. The rare association between VEGF inhibitors and cerebrovascular infarction should be considered during chemotherapy.

Adequate hydration would be necessary to maintain perfusion of the perforator area.

CONCLUSION

A cerebral infarction occurred during bevacizumab administration. This antiangiogenic agent is commonly used to treat various types of cancer, including glioblastoma multiforme. The risk of large vessel occlusion when using this compound has already been noted. Additionally, care should be taken to avoid small vessel infarction during bevacizumab administration.

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Author Contributions
Akira Tempaku – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest
Author declares no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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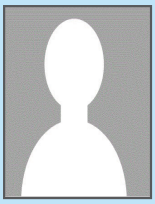

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