



Case Report

An autopsy case of widespread brain dissemination of glioblastoma unnoticed by magnetic resonance imaging after treatment with bevacizumab

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ABSTRACT

Background: Although glioblastoma has been shown to be able to disseminate widely in the intracranially after treatment with bevacizumab without any significant radiological findings, reports on such cases with subsequent autopsy findings are lacking.

Case Description: A 36-year-old man presented with a general seizure and a mass of the right frontal lobe, which was diagnosed as diffuse astrocytoma (WHO Grade II). The patient underwent a total of four surgeries from 2005 to 2017. He showed tumor recurrence, progression, and malignant transformation to glioblastoma (GBM) (WHO Grade IV) despite repeated tumor resections, radiotherapy, and chemotherapies with temozolomide and carmustine wafers. Bevacizumab (10 mg/kg body weight) was started following the fourth surgery. After bevacizumab administration, the patient's clinical condition improved to a Karnofsky performance status (KPS) score of 50–60, and he was stable for several months before finally deteriorating and passing away. Although sequential magnetic resonance imaging (MRI) showed shrinkage of the lesion and a reduction of edema, an autopsy showed widespread tumor invasion that was not revealed on MRI. Neoplastic foci were identified extensively in the cerebral cortex, basal ganglia, pituitary gland, cerebellum, and brainstem, imposing as gliomatosis cerebri.

Conclusion: Imaging follow-up of malignant gliomas needs to be interpreted with caution as marked improvement in radiological response after bevacizumab treatment may not be indicating tumor regression. Despite the notable lack of evidence to increase overall survival in GBM patients with bevacizumab, the increase in progression-free survival and the observed relief of symptoms due to a decrease in edema should be considered relevant for patient management.

Keywords: Antiangiogenesis agent, Autopsy, Bevacizumab, Brain tumor, Chemotherapy, Glioblastoma

INTRODUCTION

Glioblastoma (GBM) is the most common primary malignancy of the central nervous system in adults.^[19] It is characterized by high proliferative rate, invasiveness, angiogenicity, and insensitivity to radio- and chemo-therapy.^[1,11] GBM can appear *de novo* as a primary brain tumor

or secondarily through malignant transformation from lower grade brain tumor. Despite advancement in surgical and medical therapies, the overall prognosis of GBM patients remains poor with median survival rate of only about 15 months.^[19]

High angiogenicity in GBM is contributed by an overexpression of vascular endothelial growth factor (VEGF).^[11] Various therapeutic agents have been developed to treat GBM by targeting VEGF. Among these is Bevacizumab, which is a humanized recombinant monoclonal antibody targeting VEGF-Receptor. It has obtained accelerated approval by the United States Food and Drug Administration in May 2009.^[4] However, further clinical studies showed no improvement of overall survival (OS) in patients treated with bevacizumab compared to those receiving placebo, although progression-free survival (PFS) was prolonged in the bevacizumab group.^[2,5,6,9]

In this paper, we report a case of a patient with initial low-grade glioma who underwent a series of surgeries from 2005 to 2017 before he developed secondary GBM treated with bevacizumab. Subsequent autopsy study showed tumor invasion adjacent to the resection cavity that was not revealed in postoperative magnetic resonance imaging (MRI). The patient could maintain a relatively good clinical condition in spite of worsening disease progression. Although previous studies suggested the possibility of tumor masking in cases GBM treated with bevacizumab,^[7,15] this is the first definite study that demonstrates such a case in light of pertinent autopsy findings.

CASE REPORT

A 36-year-old man presented to our hospital in April 2005 with a general seizure. Fluid-attenuated inversion recovery (FLAIR) MRI of the brain showed a hyperintense lesion in the right frontal lobe suspicious for a low-grade glioma [Figure 1a]. The patient underwent removal of the lesion in June 2005 and the histology showed diffuse astrocytoma (WHO Grade II; mindbomb homolog [MIB]-1 index 3.5%). Postoperative radiographic examination confirmed the total removal of the entire extent of hyperintense FLAIR signal [Figure 1b].

General seizures reoccurred in 2010, 5 years after the first surgery. The seizures were not controlled with antiepileptic drugs. Radiographic reassessment at this point showed a lesion adjacent to the surgical cavity indicating recurrent tumor [Figure 1c]. In January 2011, the patient underwent the second resection in which histology revealed an oligoastrocytoma (WHO grade III; MIB-1 index 2.1%). Again, the entire extent of the FLAIR signal of the lesion was removed as confirmed on postoperative MRI [Figure 1d]. The seizures ceased postoperatively, but antiepileptic drugs were continued for another 3 months after the operation, during which the patient received adjuvant radiotherapy with a cumulative dose of 54 Gy in 27 fractions, followed by temozolomide (150 mg/m²) for 1 year.

Four years after the second surgery, seizure attacks again recurred frequently. A recurrent lesion appeared enlarging the bottom of the right frontal lobe [Figure 1e], and once

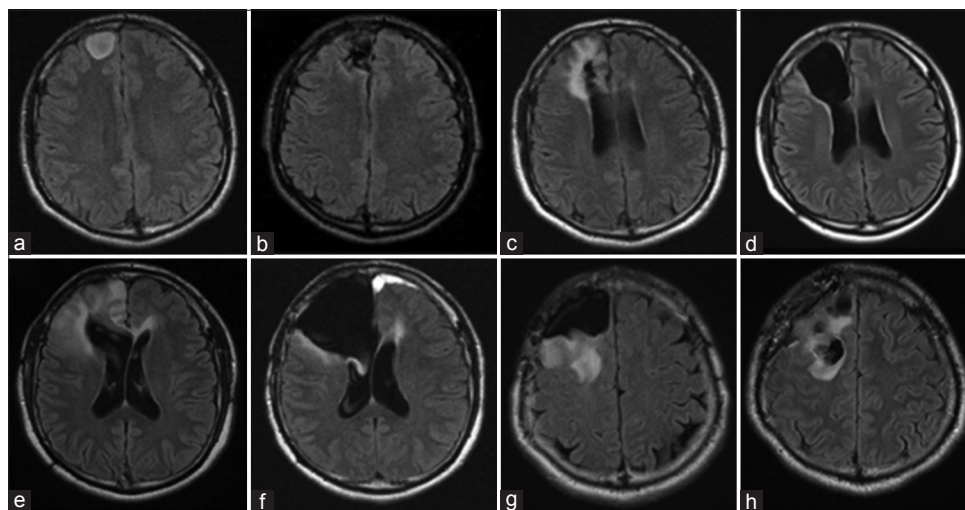


Figure 1: Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) demonstrating progression of the lesion over the patient clinical course. (a) The initial MRI before the first operation showing a hyperintense lesion in the right frontal lobe. (b) Postoperative MRI of the first surgery showing total removal of the FLAIR high lesion. (c) MRI of 5 years after the first operation demonstrating recurrence of the lesion around the removal cavity. (d) Postoperative MRI showing total removal of the recurring lesion. (e) MRI at 4 years after the second surgery showing another recurrent lesion in the right lower frontal lobe. (f) Postoperative MRI of the third surgery showing residual hyperintense lesion in the medial side of the temporal lobe. (g) MRI 2 years after the third operation showing hyperintense lesion reaching near the pyramidal tracts. (h) Carmustine wafers were placed in the removal cavity.

again, this was removed. Postoperative radiographic assessment showed partial removal of tumor with residual disease at the temporal lobe [Figure 1f]. Histopathological analysis revealed an anaplastic astrocytoma (WHO Grade III; MIB-1 index 5.1%). Temozolomide was resumed postoperatively.

Two years later, follow-up FLAIR MRI showed progression of the lesion extending toward the pyramidal tract [Figure 1g]. The patient underwent another surgery for resection. At this time, eight carmustine wafers were placed in the resection cavity. Postoperative MRI showed again subtotal removal of the tumor [Figure 1h] and temozolomide and procarbazine (100 mg for 10 days) were administered postoperatively. At this point, a histopathological diagnosis of GBM (WHO Grade IV) was made. Of note, the MIB-1 index had dramatically increased to 80%.

Approximately 8 weeks after the fourth operation, the right-sided paresis of the patient worsened and his general condition deteriorated rapidly. The Karnofsky performance status (KPS) score decreased from 70 to 50 and MRI disclosed that the lesion had progressed contralaterally. Due to the observed tumor progression, bevacizumab (10 mg/kg body weight) was given and within 1 month, the KPS score had improved to 60. The right-side hemiparesis improved. Radiological examination showed shrinkage of the lesion and decreased edema [Figure 2].

Over the course of the ensuing 5 months, bevacizumab was administered 8 times before the patient deteriorated again to terminal state with epileptic seizures occurring more frequently.

One month after hospitalization for failure to thrive, he became somnolent with unstable respirations and he developed signs of herniation. The patient was not intubated according to his living will. He died 1 h later, after a clinical course that spanned a total of 12 years.

Autopsy finding

Gross macroscopic examination

The brain weighed 1770 g, which was slightly heavier than normal. Brain edema was attributed to this finding. There was no apparent herniation identified. A surgical cavity was seen in the right frontal lobe. Black and brown masses with indistinct margins were identified in the cerebrum, ventricle, cerebellum, and brainstem.

Histopathological examination

Histopathological examination of various tumor sites revealed cells with atypically shaped nuclei [Figure 3a], anaplasia, and high proliferation [Figure 3b] corresponding

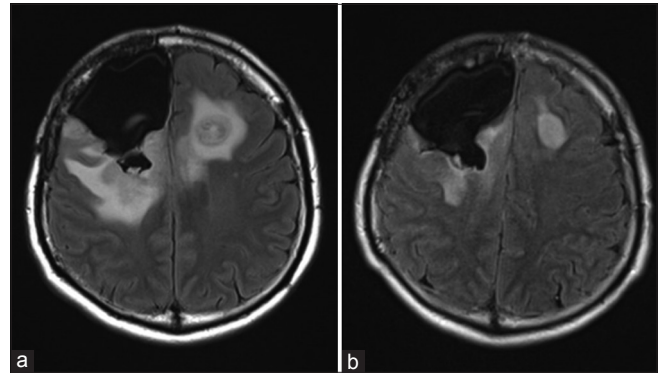


Figure 2: Axial fluid-attenuated inversion recovery magnetic resonance imaging at (a) 3 days and (b) 1 month after administration of bevacizumab. Lesion was shrunk and edema decreased.

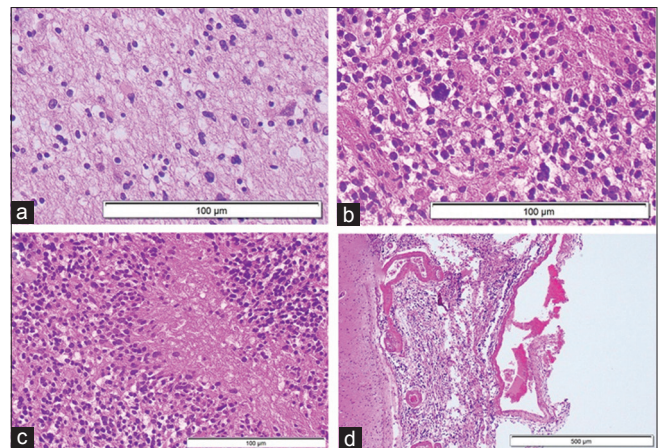


Figure 3: Microscopic finding of autopsy in hematoxylin and eosin staining. Histopathological patterns consistent with the World Health Organization (a) Grade II, (b) Grade III, and (c) Grade IV are confirmed extensively from each part of the brain. (d) Invasion also seen in the subarachnoid space at the specimen where the arachnoid membrane was removed together with the brain tissue.

to tumor areas of the WHO Grades II and III, respectively. The WHO Grade IV characteristics of palisading necrosis and mitoses were also identified [Figure 3c]. Tumor invasion was also observed in the subarachnoid space [Figure 3d]. Immunohistochemical stains were positive for isocitrate dehydrogenase-1 and negative for 1 p/19q codeletion. The Grade IV lesions were found in bilateral frontal cortices, cerebellum, brainstem, and pituitary gland. The Grade II and III lesions were widely identified around the Grade IV lesion, bilateral basal ganglia, insular cortex, and medial side of the right temporal lobe [Figures 4a and 4b]. The spread of the lesions was consistent with gliomatosis cerebri. When comparing autopsy results with MRI findings from the time after the patient had been treated with bevacizumab, it is suggested that tumor invaded areas could not be seen on MRI [Figure 4c and 4d].

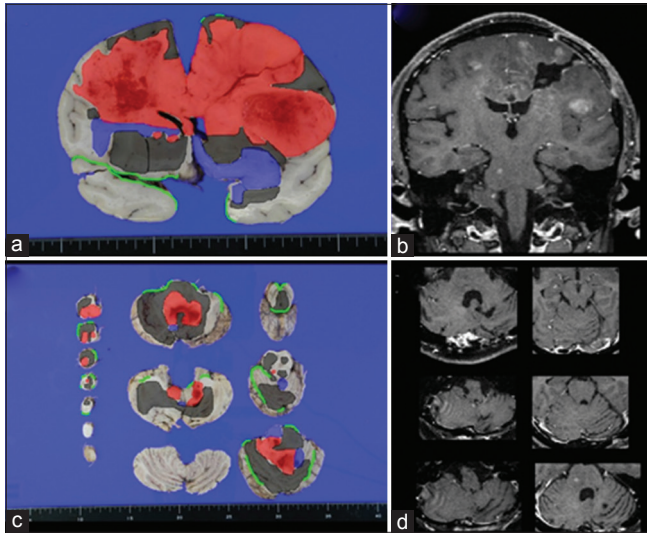


Figure 4: Superimposition of the histopathological finding on the macroscopic photography of (a) coronal slice of the cerebrum, (c) axial slices of cerebellum and brainstem from the autopsy with corresponding T1 magnetic resonance imaging (MRI) (b and d, respectively) that taken 3 months after administration of bevacizumab. Within the superimposed images, red color indicating histopathological finding consistent with the World Health Organization (WHO) Grade IV. Blue color indicating histopathological finding consistent with the WHO Grade III. Gray color indicating histopathological finding consistent with the WHO Grade II. Green line indicating subarachnoid space. Histopathological analysis revealing widespread tumor invasion in cerebrum, cerebellum, brainstem, and pituitary region that is not seen on MRI. Around the WHO Grade IV lesion, the WHO Grade II and III lesions are widely identified, except in the superolateral part of the right temporal lobe that bordering with the right frontal lobe.

DISCUSSION

As far as our knowledge, this is one of the few reported cases demonstrating invasion of GBM to brain structures at autopsy despite brain imaging showing no signs of such tumor progression after therapy with bevacizumab. Apparent tumor size and edema decreased on brain MRI, but viable tumor cells were confirmed at autopsy when the lesion had widely spread not only within the cerebral cortex but also to the basal ganglia, cerebellum, brainstem, and pituitary gland. After administration of bevacizumab, the patient's clinical condition slightly improved for a few months before final deterioration.

There is ongoing controversy regarding the use of bevacizumab to treat GBM. Bevacizumab is used to treat GBM due to its proposed ability to stop tumor expansion by inhibiting angiogenesis through VEGF pathway.^[11] Despite its promising debut, bevacizumab did not show statistically significant improvement of OS in two Phase-3 trials: Radiation Therapy Oncology Group (RTOG) and Avastin

in Glioblastoma (AVAglio) trial.^[5,9] In both studies, PFS was prolonged in patients of the bevacizumab group when compared to that seen in the placebo group. Results from Phase-2 clinical trials showed similar findings.^[2,6] Some studies reported improvement in clinical outcomes,^[2,5] while others reported ongoing deterioration of quality of life (QOL) and cognitive functions.^[9]

GBM is characterized by high angiogenic activity with abnormal tumor blood vessels. Antiangiogenic agents seem to change tumor vessels by making them less leaky, dilated, and tortuous with more normal basement membrane and greater pericytes coverage, resulting in improved vessel perfusion.^[12] This normalization of vascular function following the application of antiangiogenic drugs is also thought to reduce peritumoral edema and intracranial pressure resulting from hyperpermeability of tumor vessels.^[20]

A number of studies suggested that angiogenesis is not the only mechanism for tumors to obtain vascular supplies because tumor cells could also recruit normal blood vessel for growth – a process known as vascular cooption.^[13,16,20] This exploitation of blood vessels is not necessarily inhibited by antiangiogenic treatment and offers the tumor cells a way to invade and migrate.^[16,20] From an animal experimental study, Rubenstein *et al.* reported that increased vessel “cooption” seemed to be caused by angiogenesis inhibition.^[16] Other studies showed that angiogenesis inhibition might promote tumor cell invasiveness and formation of metastasis.^[7,15]

In this case, no tumor cells were found in the superolateral part of the right temporal lobe which was bordering the right frontal lobe where histopathological finding showed GBM. Only Grades II and III were seen in the medial part of the temporal lobe. This finding could be explained by the theory that tumor tends to spread along blood vessels or with the white matter fibers, along paths of lesser resistance.^[8] The Sylvian fissure, that separated the frontal and temporal lobes, might also limit the migration of tumor cells from the frontal lobe to the temporal lobe, while the tumor could reach the medial part of the temporal lobe through white matter fibers and blood vessel around the basal ganglia.

Normalization of tumor vascularization from bevacizumab administration appears to reduce vessel permeability and uptake of contrast-enhancing agents, thus reducing contrast enhancement usually seen in imaging modalities.^[17] This effect of antiangiogenic agents shows a rapid onset and is reversible.^[3] The marked improvement in radiographic response may not be necessarily indicative of true antitumor effects but appears attributable to decreases in contrast enhancement, hyperperfusion, and edema.^[18] While symptoms are reduced by bevacizumab, further invasion of the tumor continues, unrecognized by standard imaging modalities.

Despite an apparent lack of evidence that bevacizumab increases OS in GBM patients, the increase in PFS and the relief of symptoms due to decreased edema should be considered relevant for patient management.^[10,14] The AVAglio trial reported that bevacizumab treatment correlated with maintained KPS and a diminished glucocorticoid requirement.^[5] While the RTOG trial reported decrease in QOL in patients treated with bevacizumab, KPS and glucocorticoid requirement changes were not addressed.^[9]

As described in this case report, the patient could maintain a good clinical condition and stable KPS for several months despite widespread dissemination of the tumor after treatment with bevacizumab. This decrease in symptoms is important for activities of daily living and social interactions and translates in our opinion into QOL.

CONCLUSION

We reported an autopsy case of GBM in a patient who had been treated with bevacizumab in the terminal stage. The autopsy revealed that GBM had invaded widely in brain regions where radiological examination did not show any disease. Imaging follow-up needs, therefore, to be interpreted with caution as marked improvement in radiological responses after bevacizumab treatment may not reflect true antitumor effect. Despite lack of evidence for bevacizumab to increase OS in GBM patients, the increase in PFS and relief of symptoms due to decrease in edema appears relevant for the patient management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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