



# Diffusely Infiltrating Cerebellar Anaplastic Astrocytoma Effectively Controlled with Bevacizumab: Case Report and Literature Review

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# **Diffusely infiltrating cerebellar anaplastic astrocytoma effectively controlled with bevacizumab: case report and literature review**

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**Key words:** cerebellar glioma, bevacizumab, diffuse infiltration

## **Introduction**

Gliomas that show a gliomatosis cerebri growth pattern constitute several diffuse glioma subtypes that are characterized by exceptionally widespread involvement of three or more cerebral lobes (8). Due to the diffusely infiltrating nature and the preservation of the anatomic architecture of the surrounding normal tissues, the extent of surgical resection is usually quite limited. Therefore, these gliomas remain clinically challenging and have an extremely poor prognosis with a median survival ranging 14.5 to 18.5 months (4, 15). Gliomas with similar extensive diffuse infiltration from the cerebellum to the brainstem in the absence of cerebral cortical involvement have also been reported as an extremely rare entity. This entity was termed gliomatosis cerebelli, and to the best of our knowledge, only four cases have been described to date (3, 9, 11, 13). Given the rarity of these tumors, the clinical characteristics and prognosis of gliomatosis cerebelli are unclear, and the optimal treatment strategy is also undefined.

Bevacizumab is a humanized anti-vascular endothelial growth factor monoclonal antibody that exerts potent anti-angiogenic effects and normalization of vascular permeability (1). Administration of bevacizumab induces a decrease in contrast enhancement of the tumor and peritumoral edema on magnetic resonance imaging (MRI), leading to improved progression-free survival and maintenance of baseline quality of life (5). Based on the fundamental mechanism of the antitumor effect of bevacizumab, patients with highly neovascularized tumors are commonly considered to be good candidates for bevacizumab treatment (7). In contrast, diffusely infiltrating gliomas without a definite mass, such as gliomas with the gliomatosis cerebri growth pattern, have poor neovascularization and are expected to be less likely to respond to bevacizumab treatment. However, these issues remain uncertain because few previous

reports have discussed the efficacy of bevacizumab for gliomas with the gliomatosis cerebri growth pattern, and no reports have described diffusely infiltrating cerebellar gliomas.

We report a case of diffuse cerebellar anaplastic astrocytoma with the gliomatosis cerebelli growth pattern that was successfully controlled with bevacizumab after rapid progression during concomitant chemoradiotherapy.

### **Case report**

A 75-year-old man suffered from vertigo and headache for 2 months. He visited a nearby hospital because of the rapidly progressive nausea and dysarthria. His medical history included hypertension and atrial fibrillation. He was referred to our hospital because computed tomography revealed a relatively homogeneous low-density area in the right cerebellar hemisphere and the brainstem. On admission, neurological examination showed dysarthria, nystagmus, and right cerebellar ataxia. MRI revealed a poorly demarcated high-signal intensity on T2-weighted images and fluid-attenuated inversion recovery images in the right cerebellum and the brainstem (Fig. 1A-1, 2). The tumor in the right cerebellum showed sparse enhancement with gadolinium (Gd) on T1-weighted images (Fig. 1A-3). Magnetic resonance spectroscopy showed elevation of the choline/creatine peak ratio, a decrease in the *N*-acetyl-L-aspartic acid peak, and weak detection of the lactate signal.

Because of the rapid progression of symptoms and the severe tonsillar herniation demonstrated on MRI (Fig. 1A-5), suboccipital decompressive craniotomy and partial removal of the tumor in the right cerebellar hemisphere and cerebellar tonsil was emergently performed. The tumor component that demonstrated sparse Gd enhancement

on MRI showed positive fluorescence with intraoperative photodynamic diagnosis using 5-aminolevulinic acid; the other components showed negative fluorescence.

On histopathological examination, the tumor cells had mainly spread throughout the white matter, and were less apparent in the granular, Purkinje cellular, and molecular layers in the cerebellar cortex (Fig. 2A, B). The anatomical structures were preserved in the infiltrated white matter tissues. The tumor cells had spindle-shaped nuclei, and some nuclei showed an atypical shape (Fig. 2C, D). Little mitosis (1/10 high-power field) was seen, and no evidence of necrosis or neovascularization was present. The MIB-1 index positivity was 9% (Fig. 3A), and the tumor cells were positive for glial fibrillary acidic protein (GFAP) and S100 with immunohistochemistry. Immunohistochemical analysis also revealed retained ATRX expression but no p53 overexpression (Fig. 3B, C). The MGMT promoter methylation status as assessed by methylation-specific PCR was unmethylated. Further genomic analyses using pyrosequencing revealed no mutation in *IDH1*, *H3F3A*, or *BRAF*. The pathological diagnosis was anaplastic astrocytoma, IDH wildtype.

The patient received treatment with radiotherapy (60 Gy/30 fr) and concomitant temozolomide. However, 5 days after the start of the treatment, rapid worsening of dysarthria and dysphagia was seen. MRI that was performed 7 days after the start of the treatment showed significant enlargement of the T2 high-intensity area that extended into the cerebral peduncle and a new lesion with Gd enhancement in the midbrain (Fig. 1B).

Therefore, bevacizumab was administered at 10 mg/kg every 2 weeks beginning 11 days after the start of postoperative treatment. After administration of bevacizumab, the neurological symptoms gradually improved, the T2 high-intensity area decreased, and

the Gd-enhancing lesion disappeared, as shown on MRI (Fig. 1C). After completing concomitant chemoradiotherapy, the patient was discharged with residual symptoms of mild dysarthria and unsteadiness. Adjuvant temozolomide was administered according to the Stupp regimen for 1 year, and bevacizumab was continued every 2 weeks in the outpatient clinic. At follow-up 2 years after the operation, no worsening of the neurological symptoms was seen, and the residual T2 high-intensity area remained unchanged without detection of a new Gd-enhancing lesion on MRI (Fig. 1D).

## **Discussion**

The present case illustrates a diffusely infiltrating cerebellar anaplastic astrocytoma without a discernible mass that was effectively controlled with bevacizumab for 2 years, even after rapid progression during standard chemoradiotherapy. This case showed several remarkable features. First, this glioma with the gliomatosis cerebelli growth pattern showed rapid progression, even with standard chemoradiotherapy. Second, bevacizumab was an effective treatment for this diffuse glioma without a definite mass in the cerebellum. To the best of our knowledge, this is the first report demonstrating the efficacy of bevacizumab for a diffusely infiltrating cerebellar glioma.

The tumor in the present case was pathologically diagnosed as an anaplastic astrocytoma that diffusely involved the right cerebellum and brainstem without mass-like expansion. From the fact that H3K27M mutation which strongly supports a diagnosis of a diffuse midline glioma was not detected in genomic analysis, the most aggressive lesion represented with Gd enhancement only primarily localized in the right cerebellum, and cranial nerve dysfunction was absent as an initial symptom, the tumor may have originated in the right cerebellum and subsequently infiltrated into the

brainstem (8, 14). In this regard, the present tumor was considered to exhibit the gliomatosis cerebelli growth pattern as previously reported (3, 9, 11, 13). A diffuse glioma originating in the cerebellum and infiltrating into the brainstem, termed gliomatosis cerebelli by Rorke et al., is extremely rare, and only four cases have been reported (3, 9, 11, 13). Three reported pediatric cases showed a relatively favorable clinical course without progression following various treatments including one patient who underwent two partial resections, one patient who underwent a biopsy followed by temozolomide, and one patient who underwent partial resection followed by chemoradiotherapy (3, 9, 13). In contrast, one reported case of an elderly patient showed a poor clinical course without intensive treatment because of her low performance status (11). The present case has several similarities with the latter reported case including the elderly-onset age, positive immunoreactivity for GFAP, and clinical aggressiveness. Reported cases with gliomatosis cerebelli showed a highly variable clinical course, and a subset of such cases may progress rapidly. Likewise, a subset of gliomas with the gliomatosis cerebri growth pattern responds poorly to standard chemoradiotherapy following biopsy, leading to unfavorable outcomes (6, 12). Taken together, further investigation will be required to determine the appropriate treatment for diffuse gliomas showing the gliomatosis cerebelli or gliomatosis cerebri growth pattern, particularly in clinically aggressive cases.

Bevacizumab treatment is associated with two controversial issues about its efficacy. First is the efficacy for gliomas located in the cerebellum, and the second is for diffuse gliomas with the gliomatosis cerebri growth pattern. We previously reported no significant difference in survival time following bevacizumab treatment between patients with supratentorial recurrent malignant gliomas and those with infratentorial

recurrent malignant gliomas, suggesting the potential applicability of bevacizumab treatment for cerebellar gliomas (10). However, no other previous reports have focused on the efficacy of bevacizumab for cerebellar gliomas. With respect to the efficacy of bevacizumab for diffusely infiltrating gliomas represented by gliomas with the gliomatosis cerebri growth pattern, it seems doubtful if bevacizumab exerts therapeutic effects for those gliomas by affecting neovascularization, because diffusely infiltrating tumor cells, which are seen as non-contrast-enhancing tumors on MRI, may not depend on tumor neovasculature. In recent years, however, Burger et al. reported that diffusely infiltrating tumors do respond to bevacizumab treatment and that the effect of bevacizumab on contrast-enhancing and non-contrast-enhancing tumors was similar in most of their patient series (2). They concluded that bevacizumab should not be withheld from diffusely infiltrating gliomas because a significant proportion of patients with gliomatosis-like or non-gliomatosis-like gliomas obtain some clinical benefit from bevacizumab treatment (2). In the present case with a diffusely infiltrating anaplastic astrocytoma involving the cerebellum and the brainstem, bevacizumab provided a significant, long-term treatment effect for this aggressive tumor that showed resistance to standard concomitant chemoradiotherapy in the introduction period. Although the long-term treatment effect may be attributed to concomitant and adjuvant chemoradiotherapy with temozolomide as well as bevacizumab treatment, bevacizumab played a critical role in controlling this aggressive tumor particularly in the introduction period of standard treatment. Taken together, these findings from the present case and the previous reports indicate that bevacizumab treatment may be a salvage treatment option for patients with diffusely infiltrating cerebellar gliomas that exhibits rapid progression during standard treatment.



## **Conclusion**

Gliomas that show extensive diffuse infiltration from the cerebellum to the brainstem without a definite mass are extremely rare. Although the tumor characteristics remain uncertain due to their rarity, we should be aware that those gliomas have the potential for rapid progression due to resistance to standard chemoradiotherapy. Bevacizumab treatment may be a treatment option for this type of clinically aggressive tumor.

## Figure legends

### Figure 1

(1) Axial T2-weighted images (T2WI), (2) coronal fluid-attenuated inversion recovery images (FLAIR), (3, 4) axial T1-weighted images with gadolinium (Gd-T1WI), and (5) sagittal Gd-T1WI.

#### (A) Preoperative magnetic resonance imaging (MRI)

MRI demonstrated a poorly demarcated high-intensity lesion on T2WI and FLAIR in the right cerebellum and the brainstem. Gd-T1WI showed sparse enhancement in the tumor of the right cerebellum (short arrow) and tonsillar herniation (long arrow).

#### (B) MRI 7 days after the start of standard chemoradiotherapy treatment

MRI showed enlargement of the high-intensity area (curved arrow) and extension to the cerebral peduncle (arrowhead) on T2WI and FLAIR and new Gd enhancement in the midbrain (short arrow).

#### (C) MRI 15 days after initial administration of bevacizumab

MRI showed shrinkage of the high-intensity area on T2WI and FLAIR and disappearance of the Gd-enhancing lesion.

#### (D) MRI 2 years after the operation

MRI demonstrated no change in the residual high-intensity area on T2WI and FLAIR and no evidence of a Gd-enhancing lesion.

### Figure 2

(A, B) Photomicrographs showed tumor cells that were mainly dispersed in the white matter. (C, D) Photomicrographs demonstrated that the tumor cells have spindle-shaped

nuclei, some of which showed an atypical shape. Hematoxylin and eosin staining (A-D); magnification  $\times 12.5$  (A),  $\times 40$  (B),  $\times 100$  (C), and  $\times 400$  (D).

**Figure 3**

(A) The MIB-1 labelling index was 9%. (B) Immunohistochemical analysis showed that ATRX expression was retained. (C) Immunohistochemical analysis showed negative p53 overexpression. Magnification  $\times 100$  (A-C).

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## **Abstract**

**Background:** Gliomas that show extensive diffuse infiltration from the cerebellum to the brainstem without mass-like expansion are extremely rare. The efficacy of bevacizumab treatment for diffusely infiltrating gliomas remains uncertain.

**Case Description:** A 75-year-old man presented with a cerebellar anaplastic astrocytoma showing diffuse infiltration to the brainstem without a definite mass. He had experienced rapidly progressive nausea and dysarthria as well as vertigo and headache for 2 months. Magnetic resonance imaging (MRI) revealed a poorly demarcated T2 high-intensity area in the right cerebellum and brainstem. The tumor in the right cerebellum showed sparse enhancement with gadolinium (Gd). Suboccipital decompressive craniotomy and partial removal of the tumor was emergently performed because of the rapid progression of symptoms and the severe tonsillar herniation demonstrated on MRI. The pathological diagnosis was anaplastic astrocytoma, and genomic analyses revealed no mutation in *IDH1*, *H3F3A*, or *BRAF*. During concomitant chemoradiotherapy with temozolomide, rapid worsening of the neurological symptoms developed, and significant enlargement of the T2 high-intensity area extending to the cerebral peduncle was seen, as well as a new Gd-enhancing lesion in the midbrain. After administration of bevacizumab, the neurological symptoms gradually improved, the T2 high-intensity area decreased, and the Gd-enhancing lesion disappeared. At follow-up 2 years after the operation, no worsening of neurological symptoms was seen, and the residual T2 high-intensity area remained unchanged on MRI.

**Conclusions:** Bevacizumab treatment may be a salvage treatment option for patients with diffusely infiltrating cerebellar gliomas that exhibits rapid progression during standard treatment.







