

Case Report

Infant-type hemispheric glioma occurring at the cervicomedullary region in a 5-month-old infant: A case report with a special emphasis on molecular classification

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ABSTRACT

Background: High-grade gliomas in infancy are uncommon and have different clinical and molecular characteristics from those in adults. Recently, advances in molecular diagnostics have made progress in determining treatment strategies; however, the robust treatment has not yet been elucidated. We, herein, present a case of infantile glioma occurring at the cervicomedullary region.

Case Description: A 5-month-old infant developed left upper limb weakness and torticollis at 3 months of age. Magnetic resonance imaging revealed T2 hyperintensity from the medulla oblongata to the upper cervical cord. She underwent a biopsy for the lesion and pathological examination findings confirmed the presence of a high-grade astrocytoma with *IDH* wildtype-, *H3K27M* wildtype-, *BRAF* wildtype-, and *ETV-NTRK3* fusion-positivity. Postoperatively, she underwent chemoradiotherapy, but she had marked tumor growth during the treatment. According to the new World Health Organization classification, the patient's tumor is an infantile "hemispheric" glioma.

Conclusion: The characteristics and prognosis of *NTRK*-fused glioma are not fully understood, it is noteworthy that these tumors commonly occur in the brainstem. Further studies are needed to determine the prognosis of each tumor type and its sensitivity to treatment. This information will help in the reclassification of the tumors and identification of the precise treatment of this rare type of tumor.

Keywords: Astrocytic tumor, Cervicomedullary tumor, Glioma, Infant, *NTRK*

INTRODUCTION

High-grade gliomas (HGGs) in infants are rare, and the prevalence of astrocytoma and anaplastic astrocytoma in patients aged less than a year in Japan is reported to be 0.9% and 0.5%, respectively.^[8] Therefore, promising treatments have not been established yet. Many considerations must be made, including the role of surgery and the timing of chemotherapy and radiation therapy to obtain proper treatment for this. Recently, advances in molecular diagnosis have led to the establishment of treatment strategies by groups. However, each subtype's characteristics are not yet fully understood to establish the appropriate treatment. Here, we report a case of HGG with *NTRK* fusion occurring at the cervicomedullary junction in an infant.

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CASE ILLUSTRATION

A 5-month-old infant had no particular abnormalities at birth or any progressing disease. At 3 months of age, she was brought to a regional clinic due to poor left upper limb movement. Brain magnetic resonance imaging (MRI) demonstrated a brainstem tumor; thus, she was referred to our hospital.

At the first visit at 5 months of age, she had right torticollis and left upper limb weakness. Both anterior and posterior fontanelles were closed. Her height, weight, and head circumference were 65.8 cm (+0.5 standard deviation [SD]), 6.3 kg (−0.9 SD), and 41 cm (−0.2 SD), respectively. Brain MRI showed an intrinsic mass extending from the medulla oblongata to the upper cervical cord. The tumor appeared uniformly hypointense on the T1-weighted image and hyperintense on the T2-weighted image with heterogeneous enhancement [Figure 1]. To establish the histological diagnosis and achieve decompression of the craniovertebral junction, the patient underwent tumor biopsy with suboccipital craniotomy. Gross total resection was avoided to prevent neurological deterioration. The medulla oblongata and the cervical spinal cord were markedly swollen. Exposed soft and grayish tissue was biopsied with an incision of the left C3–C4 dorsal root exit zone.

Histopathological findings included many atypical figures of nuclear fusion despite the absence of microvascular proliferation or necrosis. Small cells proliferated densely, nuclei were unevenly distributed, and eosinophilic protrusions were observed [Figure 2]. The histopathological diagnosis was high-grade astrocytoma. An immunohistochemical study revealed a high MIB-1 labeling index of 18% and negative p53 stain. Molecular profiles showed *IDH* wildtype-, *H3K27M* wildtype-, *BRAF* wildtype-, and *ETV-NTRK3* fusion-positivity.

Based on the histological diagnosis, chemotherapy with baby Pediatric Oncology Group (POG) protocol (POG Trial 9233 Protocol) was initiated 3 weeks after the biopsy.

However, the left-sided hemiparesis progressed on the 1st day of chemotherapy, and computed tomography showed an increase in tumor size [Figure 3]. Despite decompression surgery and chemotherapy, the tumor rapidly expanded and symptoms progressed. Therefore, we started local radiotherapy; however, there were concerns about acute and late sequelae. However, after a total of 3.6 Gy of irradiation in two fractions, the tumor size further increased, resulting in obstructive hydrocephalus. She continued chemotherapy after ventriculoperitoneal shunting and tracheostomy. Despite rapid tumor growth, the deteriorating symptoms showed improvement; however, left upper and lower extremity paralysis and brainstem symptoms including dysphagia remained. Her cognitive function was normal. The tumor markedly decreased at the follow-up MRI at 15 months of age [Figure 4]. However, she died due to an upper respiratory tract infection at 25 months of age.

DISCUSSION

In this paper, we have presented a rare case of infantile glioma with *ETV-NTRK3* fusion. This case is an *ETV-NTRK3* fusion-positive tumor originating from the medullary-cervical transition zone of the medulla oblongata that grew rapidly after radiochemotherapy treatment. Cervicomedullary glioma is a rare entity, and its clinical and molecular characteristics have not been fully elucidated. To the best of our knowledge, this is the first case report of cervicomedullary glioma with *ETV-NTRK3* fusion in an infant.

According to a study that performed a literature analysis of pediatric cervicomedullary gliomas,^[10] the tumor histology was extremely diverse, including gangliogliomas, pilocytic astrocytomas, HGG, and low-grade gliomas. Surgery is the first-line treatment and chemoradiotherapy is used as a postoperative adjuvant therapy according to the clinical features of individual pathology. Furthermore, it is noted that the percentage of biopsies has increased significantly over the past 20 years, rising from 6% between 1981 and 2000 to

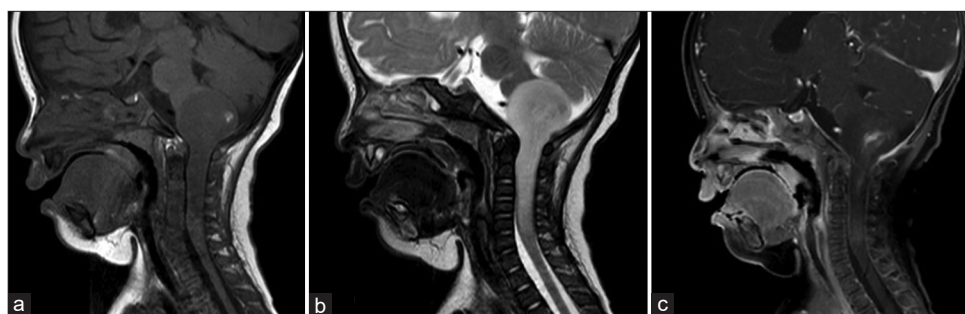


Figure 1: The initial brain magnetic resonance imaging showing a large intrinsic mass located from the medulla oblongata to the upper cervical cord. The tumor appeared uniformly hypointense on the T1-weighted image (a) and hyperintense on the T2-weighted image (b) with heterogeneous enhancement (c).

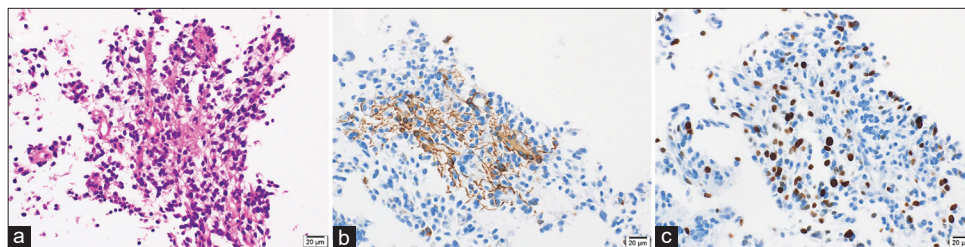


Figure 2: Histopathology showing dense small cells with atypical nuclei and eosinophilic process (a). No microvascular proliferation or necrosis was observed. Glial fibrillary acidic protein (GFAP) was positive (b) and the MIB-1 labeling index was high at 18.9% (c).

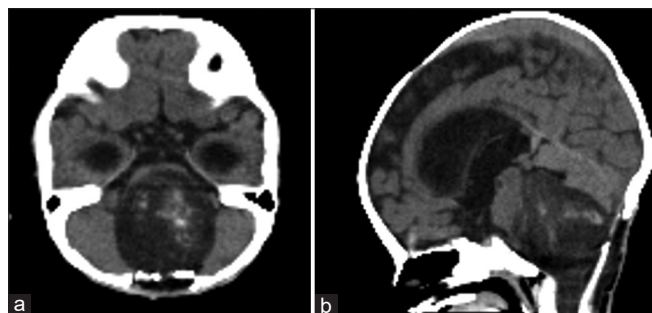


Figure 3: (a and b) Head computed tomography at 4 days after starting chemotherapy demonstrated marked enlargement of tumor.



Figure 4: Magnetic resonance imaging at 9 months of age after the treatment completion showed a decrease in the size of the cervicomedullary tumor with hyperintensity on the T2-weighted image.

25% between 2000 and 2021. This is due to advancements in molecular diagnoses and treatment, which have increased the treatment options.

Due to rapid progress in gene analysis and molecular-targeted therapies for pediatric brain tumors, it has become clear that pediatric brain tumors differ from adult tumors.

The frequency of *ALK*, *ROS1*, and *NTRK* fusion genes is relatively high in pediatric brain tumors. *NTRK* is an important protein for the nerve cell survival, differentiation, and death. Wu *et al.*^[12] reported a high prevalence of fusions involving five different N-terminal fusions with the respective kinase domains of *NTRK1*, *NTRK2*, and *NTRK3* in pediatric HGG. Furthermore, a high prevalence of positive *NTRK* fusions in infant gliomas occurring in the brainstem and midline has been reported. According to Torre *et al.*, infant and adult *NTRK* fusion gliomas were usually hemispherical, whereas pediatric *NTRK* fusion gliomas were more variable in terms of anatomical location: 38.5% (5/13), hemispheres; 23.1% (3/13), cerebellum; 23.1% (3/13), brainstem/spinal cord; 7.7% (1/13), suprasellar; and 7.7% (1/13) involved the septum pellucidum.^[9] Despite the similar molecular profile, the histopathological diagnosis varied, which included HGG, pilocytic astrocytoma, ganglioglioma, and diffuse astrocytoma, and concurrent genetic aberrations were frequently seen particularly in high-grade cases. Most *NTRK* fusion brainstem gliomas are located in the pons and rarely at the cervicomedullary region.^[5] Few studies have reported molecular profiles of cervicomedullary tumors in children. Trezza *et al.* reviewed the literature and reported ten patients with cervicomedullary glioma. However, no case of cervicomedullary glioma with *NTRK* fusion has been reported.^[10] Thus, the clinical characteristics of *NTRK* fusion glioma are still unknown, despite the identification of molecular subtypes.

The 2021 revision of the World Health Organization Brain Tumor Classification requires molecular genetic diagnosis to classify pediatric brain tumors. From a histopathological point of view, our case shows malignant findings with a mitotic figure and increased proliferative capacity in the small specimen, indicating a HGG. Based on *NTRK* gene alteration, the patient was diagnosed with an infant-type hemispheric glioma, *NTRK*-altered, despite being located in the brainstem. Infant-type hemispheric glioma is characterized by high-grade cellular astrocytoma arising in early childhood, mostly in the 1st year of life. The tumor is commonly located in the supratentorial region with a large mass and occasionally involves the adjacent leptomeninges. Despite the fact that this

entity is named “hemispheric” glioma, fusions in the *NTRK* gene are not uncommon in brainstem glioma among infants. Although the characteristics and prognosis of *NTRK*-altered infant glioma have not been fully clarified, it seems more appropriate to categorize this tumor as an infant-type glioma, rather than an infant-type “hemispheric” glioma.

In our case, symptoms progressed and the tumor grew immediately after the induction of chemoradiotherapy. It is difficult to distinguish between tumor progression and an acute response to the treatment of the tumor. The rapid deterioration of the symptoms during chemoradiotherapy could be caused by tumor progression or an acute reaction to the treatment. Because the deterioration occurred immediately after the induction of chemotherapy and radiotherapy in this case, it is more likely a side effect of either chemotherapy, radiotherapy, or both. The exact mechanism underlying the early and delayed changes after radiation therapy in brain tumors remains unclear. According to a pathology report,^[4] it is believed that blood-brain barrier (BBB) rupture, demyelination of oligos, and edema not apparent on the image are manifested, and edema after irradiation is radiosensitivity determined by genetic factors.^[3,11] Therefore, given that the dose administered to the patient was within the therapeutic range, it is possible that factors, such as low radiation resistance of the tumor, played a role. The correlation between genetic mutations and rapid progression after induction of chemoradiotherapy is unknown. However, certain types of genetic alterations might be a contributing factor because it can regulate tumor radiosensitivity.

Radiotherapy for infants should be avoided in concerns with late sequelae including cognitive dysfunction. Initially, we planned a chemotherapy-based strategy and delayed the need for radiotherapy. However, symptoms rapidly progressed after the induction of chemotherapy and the tumor was unresectable. Asheley *et al.*^[2] reported no recurrence at the irradiated site and no adverse events in patients treated with stereotactic radiotherapy after secondary resection. As no further treatment alternatives were available, we proceeded with radiotherapy. However, the development of early complications including brain swelling and long-term follow-up of late sequelae is mandatory.

The increasing number of cases has resulted in the widespread use of molecular diagnosis and treatment with molecular-targeted drugs with favorable results.^[1,6,7] In the molecular era, timely and efficient genetic analysis is essential for therapeutic decision-making, and further, collection of data is required for this.

CONCLUSION

We reported a rare case of infantile glioma at the cervicomedullary region with *ETV-NTRK3* fusion- and

H3K27M wildtype-positivity. Recent advancement in genetic analysis enabled us to establish a new classification of brain tumors based on molecular profile. However, the characteristics of pediatric gliomas, including each molecular subtype, are still unknown, and further, research is required to clarify the prognosis and sensitivity against treatment of each tumor type. These details of our case will be useful for tumor reclassification and establishing precision treatment for this rare type of tumors.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author(s) confirms that there was no use of Artificial Intelligence (AI)-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using the AI.

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