doi: 10.2176/jns-nmc.2024-0189

NMC Case Report Journal 11, 427-433, 2024

Three Years of Progression-free after Biopsy of BRAF V600E-negative Ganglioglioma in the Adult Brainstem: A Case Report and the Literature Review

Toshiki ISHIKURA,[1] Seiichiro HIRONO,[1] Masayuki OTA,[2] Daiki YOKOYAMA,[1] Masayoshi KOBAYASHI,[1] Tomoo MATSUTANI,[1] and Yasuo IWADATE[1]

[1]*Department of Neurological Surgery, Chiba University Graduate School of Medicine, Chiba, Chiba, Japan*
[2]*Diagnostic Pathology, Chiba University Graduate School of Medicine, Chiba, Chiba, Japan*

Abstract

Ganglioglioma, a glioneuronal neoplasm, typically presents in adolescents' temporal lobes. While pediatric brainstem gangliogliomas (BSGGs) are well documented, adult BSGGs are limited, resulting in a lack of comprehensive understanding of their pathophysiology and prognosis. A 41-year-old woman who presented with dizziness and numbness in her right upper extremity and right face underwent radiological examination. A dorsally exophytic tumor in the medulla oblongata was identified. Moderate uptake of ^{11}C-methionine on positron emission tomography suggests a low-grade glioma. Histopathological evaluation, following a suboccipital craniotomy and biopsy under neuromonitoring, confirmed the tumor as a mix of neoplastic ganglion cells and glial cells, which exhibited immunoreactivity for chromogranin A and OLIG2, respectively. Eosinophilic granular bodies and Rosenthal fibers were also observed. These findings confirmed the diagnosis of a ganglioglioma. The BRAF V600E mutation tested negative by real-time polymerase chain reaction. No postoperative adjuvant treatment was administered, and no progression of the residual tumor was noted 34 months post-surgery. Increased reporting of adult BSGGs, complete with detailed radiological, molecular, and genetic profiles, as well as their clinical course, is essential for clarifying our understanding of this rare entity's oncogenic pathway, optimal management strategy, and prognosis.

Keywords: ganglioglioma, BRAF V600E, brainstem

Introduction

Gangliogliomas (GGs) are relatively rare glioneuronal neoplasms composed of both neoplastic ganglion and glial cells. Cerebral GGs frequently manifest with seizures, with the severity of initial symptoms being determined by the tumor's size and location. GGs can develop throughout the central nervous system (CNS) including the brainstem, cerebellum, and spinal cord. In one of the largest case series[1)] which included 886 GGs, more than 80% were localized in the temporal lobes. The cerebellum and brainstem are the second and third most common locations for GGs in pediatric populations,[2)] with frequencies of 6.3% and 3.7%, respectively. Adult brainstem GGs (aBSGGs) are, however, exceedingly rare. To the best of our knowledge, less than 50 adult cases of BSGGs have been reported since 2010. Therefore, the clinical and radiological features are poorly understood, resulting in difficult preoperative diagnosis and uncertain prognosis. Recently, metabolic imaging with ^{11}C-methionine positron emission tomography (Met-PET) was used for preoperative diagnosis in patients with brain neoplasms.[3)] However, the metabolic profiles that could distinguish BSGGs from other brainstem tumors and non-tumoral lesions, are still lacking.

Furthermore, a histopathological definition of GGs has not yet been established. The 2016 World Health Organization (WHO) classification described GGs as a combination of dysplastic ganglion cells and neoplastic glial cells, cate-

Received July 25, 2024; Accepted October 10, 2024

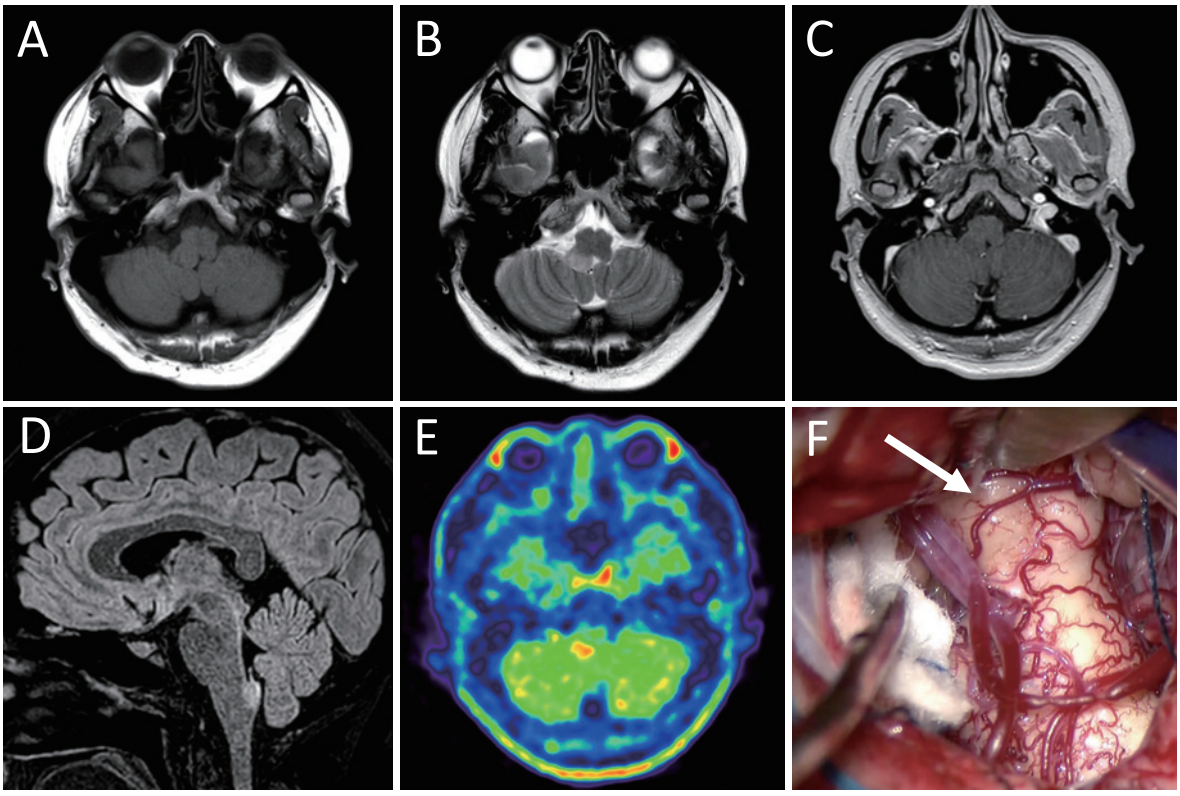

Fig. 1 Preoperative axial T1-weighted (A), T2-weighted (B), and T1-weighted imaging with contrast enhancement (C). Sagittal fluid-attenuated inversion recovery imaging (D) and metabolic imaging with ^{11}C-methionine positron emission tomography (E). Intraoperative image (F) demonstrating the protrusion of the dorsal surface of the medulla oblongata (arrow).

gorizing them as grade I or grade III based on anaplastic features, including increased cellularity, pleomorphism, and increased numbers of mitotic figures. However, the 2021 WHO classification defined GGs as slow-growing, well-differentiated glioneural tumors composed of neoplastic ganglions and glial cells. Recently, genetic alterations activating the mitogen-activated protein kinase (MAPK) pathway have been identified in GG tumorigenesis. Accordingly, the 2021 classification[4] clearly highlighted these genetic alterations causing MAPK pathway activation. Among these, BRAF V600E mutation is found in approximately 50% GG cases across all anatomical locations.[5] However, its role in aBSGG prognosis remains unclear. Therefore, more cases with detailed histopathological and genetic information, as well as oncological outcomes, are needed.

Additionally, there is no established optimal management strategy for BSGGs. Despite the extensive exploration of safe entry zones into the brainstem for microsurgical procedures,[6] this area still presents significant surgical challenges. Consequently, it is essential to clarify the oncological and functional outcomes of microsurgical resection of BSGGs. Given the increasing use of molecular-targeted therapies for brain tumors, including GGs, the importance of histological diagnosis and genetic profiling extends to brainstem tumors. The prognosis of aBSGGs remains poorly understood, mainly due to the limited number of cases reported and short follow-up periods.

Herein, we report a case of aBSGG with radiological, immunohistochemical, and genetic data, as well as details of the postoperative clinical course, to facilitate knowledge dissemination regarding this rare tumor.

Case Report

Clinical history, operation, and postoperative course

A 41-year-old woman presented at a local hospital with intermittent dizziness persisting over several years. She also experienced numbness in her right hand and face, occasionally accompanied by headaches. These symptoms, varying in duration from several mins to an hr, would resolve spontaneously. Cerebral magnetic resonance imaging (MRI) revealed signal abnormalities in the dorsal medulla oblongata, prompting a referral to our institution. Further MRI investigations revealed a solid mass in the right medulla oblongata with a posterior exophytic protrusion. The lesion exhibited an isointense signal on T1-weighted imaging and a hyperintense signal on T2-weighted and FLAIR images, with no cyst formation or contrast enhancement (Fig. 1A-D). No calcification was observed on computed tomography (not shown). Notably, no abnormal findings were detected in the brain MRI images obtained 10 years prior (data not shown). Met-PET imaging revealed moder-

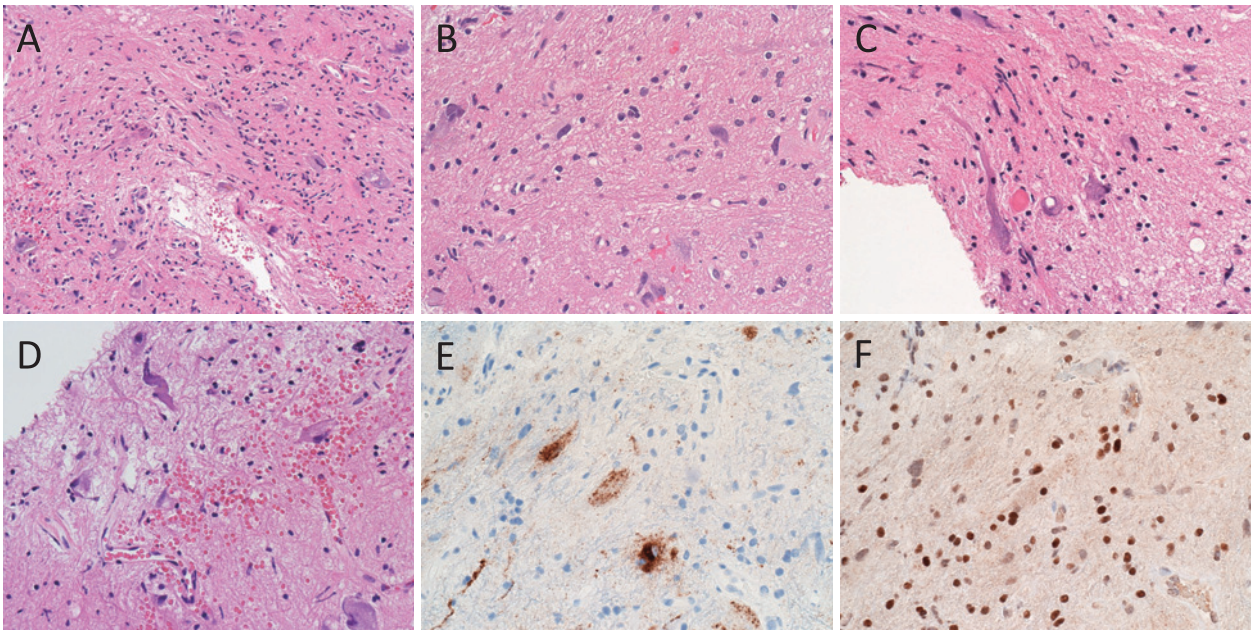

Fig. 2 Pathology of the resected specimen. Hematoxylin and eosin staining (A, B) comprising both neoplastic ganglion and glial cells (A and B). Eosinophilic granular bodies (C) and Rosenthal fibers (D) were observed in the magnified photomicrograph. Chromogranin A immunostaining (E), a neuronal marker, was positive for neoplastic ganglion cells. OLIG2 immunostaining (F), a glial marker, highlighted the glial component.

ate uptake of ^{11}C-methionine with a Tmax/Nave value of 2.0 (Fig. 1E), suggesting low-grade gliomas. The preoperative radiological differential diagnoses included ganglioglioma, pilocytic astrocytoma, and ependymoma. The patient underwent suboccipital craniotomy. After dural opening, dissection around the caudal loop of the right posterior inferior cerebellar artery facilitated the elevation of the right cerebellar tonsil, and the protrusion of the dorsal surface of the medulla oblongata was clearly identified (Fig. 1F). Electrical stimulation confirmed the preservation of the brainstem nuclei, followed by minimal coagulation and sharp incision of the prominent floor of the fourth ventricle. Tissue samples were obtained piecemeal. The postoperative course was uneventful. Mild cerebellar ataxia manifested on the first postoperative day but completely subsided within a few days. Dizziness also improved during the postoperative follow-up visits. No adjuvant treatments were administered, and the residual tumor showed no progression 34 months postoperatively.

Histopathological, immunohistochemical, and genetic findings

Histopathological examination of the specimen revealed a combination of neoplastic ganglion and glial cells (Fig. 2A and B). Eosinophilic granular bodies (Fig. 2C) and Rosenthal fibers (Fig. 2D) were also observed in the magnified photomicrographs. The neoplastic ganglion cells were positive for chromogranin A immunostaining (Fig. 2E), a neuronal marker. In addition, OLIG2 immunostaining (Fig. 2F), a glial marker, revealed a glial component. Increased cellularity and number of mitotic figures confirmed the histological diagnosis of a WHO grade 1 ganglioglioma. Real-time polymerase chain reaction (RT-PCR) testing revealed the absence of BRAF V600E mutations.

Discussion

Low-grade brainstem gliomas typically exhibit discrete, well-circumscribed masses with clear margins. Additionally, an exophytic pattern of growth and absent or minimal post-contrast enhancement are common. Tectal gliomas and GGs are representative pediatric low-grade gliomas of the brainstem. However, adult GGs in the brainstem are remarkably rare, with fewer than 50 adult cases of BSGGs have been reported since 2010. Ipsilateral cerebellar cortical atrophy (ICCA) is suggestive of infratentorial GGs.[7] Zhang et al.[8] reported that ICCA are more frequently observed in BSGGs than in cerebellar GGs. As our case of adult BSGG displayed no signs of ICCA (Fig. 1A-D), gathering more cases with detailed imaging findings is necessary to validate this hypothesis. Metabolic evaluations using Met-PET may aid in the preoperative diagnosis of BSGGs. In cases with supratentorial epileptogenic tumors, Met-PET was reported to be useful for distinguishing between dysembryoplastic neuroepithelial tumors and ganglioglioma.[9] However, little is known about the diagnostic reliability of Met-PET for brainstem GGs. In our case, moderate accumulation of Met was observed, aligning with a previous report of supratentorial GGs.[10] Interestingly, Pan et al.[11] reported a possible relationship between radiologi-

Table 1 Frequency of *BRAF* V600E mutation in adult patients with ganglioglioma in all anatomical location

Publication	Total number of adult patients	Number of patients with *BRAF* V600E mutation	Frequency of *BRAF* V600E mutation, %
Schindler et al.,[14] 2011	53	11	21
Chappe et al.,[15] 2013	3	1	39
Koelsche et al.,[18] 2013	41	19	46
Qin et al.,[20] 2014	1	1	100
Donson et al.,[5] 2014	2	1	50
Gupta et al.,[21] 2014	3	1	33
Gessi et al.,[22] 2016	3	0	0
Chen et al.,[23] 2017	12	6	50
Pekmezci et al.,[25] 2018	21	8	38
Total	139	47	34

Table 2 Frequency of *BRAF* V600E mutation in adult BSGG

Publication	Total number of adult* BSGG patients	Number of patients with *BRAF* V600E mutation	Frequency of *BRAF* V600E mutation, %
Qin et al.,[20] 2014	1	1	100
Chen et al.,[23] 2017	12	6	50
Our case	1	0	0
Total	14	7	50

*Adult patients (aged >18 years).
BSGG: brainstem ganglioglioma

cal growth patterns and tumor recurrence in BSGGs. They classified BSGGs into 3 categories—exophytic, intrinsic, and endo-exophytic—and found that all recurrent BSGGs had an endo-exophytic morphology. This hypothesis has been validated in a past case report.[12] The authors speculated that a smaller extent of resection in endo-exophytic BSGGs was associated with a high risk of recurrence. However, additional cases with sufficient molecular profiles, MRI data, and oncological outcomes are required to confirm these findings.

In our literature review, adult (aged >18 years) GG patients with various CNS locations were identified in the PubMed database using a combination of search terms including "ganglioglioma" "adult" since 2010. This review only included full-text articles written in English, with sufficient clinical data available. The following data were collected for each patient: sex, age at diagnosis, tumor anatomical location, tumor morphology, radiological features, extent of resection, histological grade, BRAF V600E mutation status, adjuvant therapy, and disease control outcomes. In this literature search, we identified 499 GG patients in all anatomical locations and ages with obvious BRAF status[5,11,13-26] and found that 202 out of 499 patients with GG harbored BRAF V600E mutation (40%). Among those, 139 adult GG patients with known BRAF status are shown in Table 1. In addition, we focused on BSGGs in an adult subpopulation, and a total of 39 aBSGGs were found in the literature, regardless of BRAF status.[8,20,23,27-29] In those, the median age at aBSGG diagnosis was 33 years (range, 18-52 years). Overall, females were more frequently affected than males, with a male-to-female ratio of 1:1.4. The most common symptoms were limb weakness, ataxia, and sensory abnormalities, followed by dizziness, dysphagia, headache, and hoarseness. aBSGGs were most commonly located at the cervicomedullary junction (n = 15), followed by the medulla oblongata (n = 14) and the pons. Conversely, there were very few reports on GGs in the midbrain. Of the 39 cases of aBSGGs, the actual figures of MRI images were available for only 9 cases.[8,20,23,27-29] Based on these findings, the radiological appearance varied greatly, ranging from solid tumors to cystic components. Cyst formation was observed in only 3 cases. Exophytic growth pattern was found in 6 out of 9. Partial contrast enhancement was observed in some cases but was not definitive. Met-PET was only conducted in our case, showing moderate methionine uptake. Most reported cases were grade 1 GGs. However, 2 grade 2 cases and one grade 3 case have also been reported.

When focusing on BRAF V600E status, only 13 of 39 aBSGG had satisfactory data on BRAF status[20,23] (Table 2). We revealed that 7 out of 13 cases with aBSGG harbored

V600E mutation on BRAF gene with a frequency of 53%. Similarly, another literature search identified 24 of 52 (46%) pediatric BSGGs had this mutation.[5,15,21,23,24] As mentioned above, 202 of 499 patients with GG harbored this mutation (40%), regardless of patients' age and the tumor location.[5,11,13-26] The similar rate of this genetic alteration in different location and age subgroups, suggested that the majority of GGs may share similar underlying genetic alterations, particularly in BRAF gene. Due to limited data regarding the disease control period, no oncological outcomes, including progression-free survival (PFS), were calculated.

We identified that 2 age groups, aBSGGs, and pediatric BSGGs, share the main radiological and genomic characteristics. Lindsay et al.[19] reported that 9 out of 11 pediatric posterior fossa GG (majority of them were brainstem GGs) demonstrated solid masses. In our review of 39 aBSGGs, regardless of BRAF status, the radiological features were available only in 16 cases. The most common radiological finding was solid, which was found in 11 of 16 aBSGGs. These suggest that no significant difference in radiological characteristics in adult and pediatric BSGGs. As for BRAF mutation, we already mentioned that adult and pediatric BSGGs shared the similar frequency of BRAF V600E mutation (53% and 46%, respectively). This similarity suggest that adult and pediatric BSGGs may have the similar pathogenetic background. Unfortunately, we could not clarify the difference in prognosis due to limited follow-up data, especially in aBSGGs. In our review of 39 aBSGGs, 16 cases lacked the control status of the residual tumor. The disease progression was observed in 9 out of the remaining 23 aBSGGs. However, the exact period of PFS was not provided in the majority of the literature. In contrast, the PFS period in pediatric BSGGs was 8.8 months[16] and 1.2-1.7 years.[19] The accumulation of aBSGG cases with enough PFS data is necessary to clarify the difference of disease prognosis in age subgroups.

When comparing the MR findings between BSGGs and supratentorial GGs in adult populations,[7] no critical difference was found in the literature. As for supratentorial GGs, solid (50%) and cystic-solid (42%) appearance were the common demographic features. However, as we mentioned, 11 of 16 (69%) aBSGGs demonstrated solid component.

According to the report of 19 adult supratentorial GGs by Pekmezci et al.,[25] the majority of those achieved the gross total resection (GTR). Seven of 19 patients (37%) harbored BRAF V600E mutation, and the disease progression was observed only in 2. Considering the anatomical challenges for GTR in BSGGs, the supratentorial GGs in adults have better prognosis than aBSGGs. However, detailed genetic profiles especially in aBSGGs are necessary to clarify the prognostic influence in both locations.

Recently, genetic alterations causing the activation of the MAPK pathway have been identified for the tumorigenesis of GGs, resulting in the definition of GGs in the 2021 WHO classification.[4] A representative genetic aberration is a missense mutation in codon 600 of the BRAF gene, as previously mentioned, which results in a change from glutamic acid to valine at amino acid 600 within the P-loop of the serine/threonine kinase domain. The BRAF V600E mutation has been widely identified in patients with GGs. Chen et al.[23] reported that the BRAF V600E mutation is a significant prognostic factor for tumor progression in BSGGs. Among 18 patients with BSGG (12 adult and 6 pediatric BSGGs), the subgroup with the mutant BRAF V600E showed a shorter PFS period than those with the wild-type variant. More specifically, 4 out of 6 aBSGGs with mutated BRAF demonstrated progression of the residual tumor. In contrast, only 2 out of 6 aBSGGs with wild-type BRAF gene showed increased residue. However, the more aBSGG cases with enough PFS data and BRAF status are essential to clarify the influence of BRAF V600E in disease progression. Donson et al.[5] also reported that BRAF V600E is a negative prognostic factor in pediatric BSGGs concerning both PFS and overall survival. In our case, BRAF V600E was not detected using RT-PCR, and the tumor remained stable without progression for 34 months after surgery without adjuvant therapy, which is consistent with previous reports. However, a longer follow-up is required to validate these hypotheses. It is worth mentioning that this mutation has no prognostic influence on non-brainstem GGs.[25] We speculate that this is because most of supratentorial GGs can be completely resected.

Recently, Pekmezci et al.[25] reported that GGs without BRAF V600E often harbor other oncogenic mutations in the BRAF gene or activation of the MAPK pathway, including recurrent small in-frame insertions at codon p.R506, BRAF-KIAA1549 gene fusion, RAF1 gene fusions, KRAS mutations, and inactivation NF1 mutations. Notably, 90% of GGs in their cohort were identified to have genetic alterations predicted to activate the MAPK pathway. As long as we reviewed, no meticulous genetic explorations other than BRAF V600E have been performed in aBSGGs, probably because of the limited number of cases and tissue samples. These data will contribute to a better understanding of pathophysiology and possible treatment strategies for BSGGs.

Pan et al.[11] reported a potential link between tumor form and prognosis. They categorized 21 BSGGs into 3 types: exophytic (n = 2), intrinsic (n = 6), and endo-exophytic (n = 13), and found that all the recurrence (n = 4) was in the endo-exophytic group. Interestingly, endo-exophytic BSGGs showed more frequent involvement of critical structures, including the obex and vagal triangle. This could result in a less extensive resection and a poorer prognosis. They also showed that all recurrent tumors, except one lacking sufficient molecular information, carried the BRAF V600E mutation. More extensive case series are needed to clarify the prognostic impact of BRAF status

and tumor morphology.

There is currently no standard treatment strategy for BSGGs due to their rare occurrence, challenging location, and our limited understanding of their natural history and prognosis. In our case, only a biopsy was conducted, and aggressive resection was not attempted. Generally, dorsally exophytic brainstem tumors with good surgical accessibility are the best candidates for surgical intervention. Surgical resection of exophytic BSGGs is associated with good functional outcomes.[11] Clarifying the molecular profiles of brain tumors is desirable for pathological classification, treatment selection, and prognostic prediction. Because liquid biopsy of circulating tumor cells in patients with brain tumors, including BSGGs, is not well established, surgical intervention and tumor sampling remain crucial. Currently, tumor control and favorable functional outcomes following aggressive resection of BSGGs are insufficient. Further studies on the extent of resection and detailed functional outcomes are required.

In conclusion, this report emphasizes the utility of Met-PET in the preoperative management of brainstem lesions. A biopsy of a dorsally exophytic tumor in the medulla confirmed the histological diagnosis of ganglioglioma with excellent functional outcomes. RT-PCR revealed no BRAF V600E mutations and no tumor progression was observed for 34 months without adjuvant therapy. A larger number of reports including adult and pediatric BSGGs with detailed information on genetic alterations will aid in better understanding of tumorigenesis, radiological characteristics, surgical and nonsurgical management, and prognosis of BSGGs. These data provide vital information that can drive efforts to understand disease burden and improve the outcome for individuals with aBSGGs.

Ethical Approval

Ethical approval was not applicable to this case report.

Consent for Publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflicts of Interest Disclosure

All authors have no conflict of interest.

References

1) Slegers RJ, Blumcke I: Low-grade developmental and epilepsy associated brain tumors: a critical update 2020. *Acta Neuropathol Commun* 8: 27, 2020
2) Dudley RW, Torok MR, Gallegos DR, et al.: Pediatric low-grade ganglioglioma: epidemiology, treatments, and outcome analysis on 348 children from the surveillance, epidemiology, and end results database. *Neurosurgery* 76: 313-319; discussion 319; quiz 319-320, 2015
3) Yamaki T, Higuchi Y, Yokota H, et al.: The role of optimal cut-off diagnosis in 11C-methionine PET for differentiation of intracranial brain tumor from non-neoplastic lesions before treatment. *Clin Imaging* 92: 124-130, 2022
4) WHO Classification of Tumours Editorial Board: WHO classification of tumours: central nervous system tumours, ed 5. Lyon, International Agency for Research on Cancer, 2021
5) Donson AM, Kleinschmidt-DeMasters BK, Aisner DL, et al.: Pediatric brainstem gangliogliomas show BRAF(V600E) mutation in a high percentage of cases. *Brain Pathol* 24: 173-183, 2014
6) Cavalcanti DD, Preul MC, Kalani MY, Spetzler RF: Microsurgical anatomy of safe entry zones to the brainstem. *J Neurosurg* 124: 1359-1376, 2016
7) Lou X, Gui QP, Sun L, Wu NZ, Lyu JH, Ma L: Comparisons of MR Findings Between Supratentorial and Infratentorial Gangliogliomas. *Clin Neuroradiol* 26: 65-71, 2016
8) Zhang S, Ai L, Chen XZ, Wang K: Radiological evaluation of infratentorial gangliogliomas in various anatomic locations of the cerebellum and brainstem. *Clin Neuroradiol* 27: 319-327, 2017
9) Rheims S, Rubi S, Bouvard S, et al.: Accuracy of distinguishing between dysembryoplastic neuroepithelial tumors and other epileptogenic brain neoplasms with [(1)(1)C]methionine PET. *Neuro Oncol* 16: 1417-1426, 2014
10) Rosenberg DS, Demarquay G, Jouvet A, et al.: [11C]-Methionine PET: dysembryoplastic neuroepithelial tumours compared with other epileptogenic brain neoplasms. *J Neurol Neurosurg Psychiatry* 76: 1686-1692, 2005
11) Pan CC, Chen X, Xu C, et al.: Brainstem gangliogliomas: prognostic factors, surgical indications and functional outcomes. *J Neurooncol* 128: 445-453, 2016
12) Rush S, Foreman N, Liu A: Brainstem ganglioglioma successfully treated with vemurafenib. *J Clin Oncol* 31: e159-e160, 2013
13) Dougherty MJ, Santi M, Brose MS, et al.: Activating mutations in BRAF characterize a spectrum of pediatric low-grade gliomas. *Neuro Oncol* 12: 621-630, 2010
14) Schindler G, Capper D, Meyer J, et al.: Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. *Acta Neuropathol* 121: 397-405, 2011
15) Chappe C, Padovani L, Scavarda D, et al.: Dysembryoplastic neuroepithelial tumors share with pleomorphic xanthoastrocytomas and gangliogliomas BRAF(V600E) mutation and expression. *Brain Pathol* 23: 574-583, 2013
16) Dahiya S, Haydon DH, Alvarado D, Gurnett CA, Gutmann DH, Leonard JR: BRAF(V600E) mutation is a negative prognosticator in pediatric ganglioglioma. *Acta Neuropathol* 125: 901-910, 2013
17) Ramkissoon LA, Horowitz PM, Craig JM, et al.: Genomic analysis of diffuse pediatric low-grade gliomas identifies recurrent oncogenic truncating rearrangements in the transcription factor MYBL1. *Proc Natl Acad Sci U S A* 110: 8188-8193, 2013
18) Koelsche C, Wohrer A, Jeibmann A, et al.: Mutant BRAF V600E protein in ganglioglioma is predominantly expressed by neuronal tumor cells. *Acta Neuropathol* 125: 891-900, 2013
19) Lindsay AJ, Rush SZ, Fenton LZ: Pediatric posterior fossa ganglioglioma: unique MRI features and correlation with BRAF V600E mutation status. *J Neurooncol* 118: 395-404, 2014
20) Qin B, Tabbara AK, Delalle I, Holsapple J, Hohler A: An enig-

matic brainstem posterior fossa ganglioglioma in an adult. *Int J Neurosci* 124: 704-706, 2014
21) Gupta K, Orisme W, Harreld JH, et al.: Posterior fossa and spinal gangliogliomas form two distinct clinicopathologic and molecular subgroups. *Acta Neuropathol Commun* 2: 18, 2014
22) Gessi M, Dorner E, Dreschmann V, et al.: Intramedullary gangliogliomas: histopathologic and molecular features of 25 cases. *Hum Pathol* 49: 107-113, 2016
23) Chen X, Pan C, Zhang P, et al.: BRAF V600E mutation is a significant prognosticator of the tumour regrowth rate in brainstem gangliogliomas. *J Clin Neurosci* 46: 50-57, 2017
24) Pages M, Beccaria K, Boddaert N, et al.: Co-occurrence of histone H3 K27M and BRAF V600E mutations in paediatric midline grade I ganglioglioma. *Brain Pathol* 28: 103-111, 2018
25) Pekmezci M, Villanueva-Meyer JE, Goode B, et al.: The genetic landscape of ganglioglioma. *Acta Neuropathol Commun* 6: 47, 2018
26) Stone TJ, Keeley A, Virasami A, et al.: Comprehensive molecular characterisation of epilepsy-associated glioneuronal tumours. *Acta Neuropathol* 135: 115-129, 2018
27) Gonzalez Toledo E, Nader M, Thomas-Ogunniyi J, Wilson J: Anaplastic ganglioglioma of the brainstem in an adult. *Neuroradiol J* 25: 325-329, 2012
28) Zhang S, Wang X, Liu X, Ju Y, Hui X: Brainstem gangliogliomas: a retrospective series. *J Neurosurg* 118: 884-888, 2013
29) Janjua MB, Ivasyk I, Pisapia DJ, Souweidane MM: Ganglioglioma of brain stem and cervicomedullary junction: a 50 years review of literature. *J Clin Neurosci* 44: 34-46, 2017

Corresponding author: Seiichiro Hirono, MD, PhD
Department of Neurological Surgery, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo, Chiba, Chiba 260-8670, Japan.
e-mail: s-hirono@chiba-u.jp