Case Report

Long-term survival of a patient with diffuse midline glioma in the pineal region: A case report and literature review

Takahiro Ono1, Haruka Kuwashige1, Jun-Ichi Adachi2, Masataska Takahashi1, Masaya Oda1, Toshihiro Kumabe3, Hiroaki Shimizu1

1Department of Neurosurgery, Akita University Graduate School of Medicine, Akita, 2Department of Neuro-Oncology/Neurosurgery, Saitama Medical University International Medical Center, Hidaka, 3Department of Neurosurgery, Kitasato University School of Medicine, Sagamihara, Japan.

E-mail: *Takahiro Ono - t.ono@med.akita-u.ac.jp; Haruka Kuwashige - h828kmoya14ci@gmail.com; Jun-Ichi Adachi - jadachi@saitama-med.ac.jp; Masataska Takahashi - masataka@med.akita-u.ac.jp; Masaya Oda - mod@med.akita-u.ac.jp; Toshihiro Kumabe - kuma@kitasato-u.ac.jp; Hiroaki Shimizu - nshrk@med.akita-u.ac.jp

*Corresponding author: Takahiro Ono, Department of Neurosurgery, Akita University Graduate School of Medicine, Akita, Japan.
t.ono@med.akita-u.ac.jp

Received : 15 November 2021
Accepted : 24 November 2021
Published : 14 December 2021

ABSTRACT

Background: Diffuse midline glioma (DMG) is an invasive astrocytic tumor arisen from midline structures, such as the pons and thalamus. Five cases of DMG in the pineal region have been reported, but the clinical course was poor; there was no case of survival for more than 2 years.

Case Description: We report the case of a 12-year-old boy with DMG in the pineal region who is living a normal daily life for more than 6 years following multimodal treatment. He complained of a headache accompanied by vomiting that had gradually worsened 1 month previously, and initial magnetic resonance imaging revealed a pineal tumor. Germinoma was initially suspected; however, a combination of chemotherapy using carboplatin and etoposide was ineffective. The first surgery was performed through the left occipital transtentorial approach (OTA); the diagnosis was DMG. After 60 Gy radiotherapy concomitant with temozolomide (TMZ), the tumor enlarged. Second surgery was performed through bilateral OTAs, and 90% of the tumor was removed. In addition, stereotactic radiotherapy (30 Gy, six fractions) was administered, and the local equivalent dose in 2 Gy/fraction reached 97.5 Gy. Maintenance chemotherapy using TMZ and bevacizumab was continued for 2 years. After finishing chemotherapy, the enhancing lesion enlarged again, and bevacizumab monotherapy was effective. Now, at 6 years after diagnosis, the patient leads an ordinary life as a student.

Conclusion: Maximum resection and high-dose radiotherapy followed by bevacizumab may have been effective in the present case.

Keywords: Bevacizumab, Diffuse midline glioma, High-dose radiotherapy, Maximum resection, Pineal tumors

INTRODUCTION

Diffuse midline glioma (DMG) commonly develops in midline structures, such as the pons and thalamus, and is molecularly characterized by H3.3 or H3.1 K27M mutation. The effect of radiotherapy is limited; there is no established chemotherapy, and the 2-year survival rate is <10%. Five cases of DMG in the pineal region have been reported, with no cases of survival for more than 2 years.
We herein report the case of a patient with DMG extended to the pineal region who has lived for more than 6 years following multimodal treatment.

**CASE DESCRIPTION**

A 12-year-old boy, who had no notable medical, family, or psychosocial history, presented with headache and vomiting. Magnetic resonance imaging (MRI) revealed hydrocephalus and a pineal region tumor with a major axis of 34 mm. Serum levels of alpha-fetoprotein and beta-human chorionic gonadotropin were within the normal range. Initially, the tumor was suspected of germinoma; hence, endoscopic biopsy and third ventriculostomy were performed. Although hydrocephalus improved, histological diagnosis could not be obtained.

Combination chemotherapy using carboplatin and etoposide was administered as a diagnostic treatment. However, the tumor had grown 1 month after (maximum diameter, 46 mm) [Figure 1a and b], for which the patient underwent surgical resection.

Preoperative three-dimensional computed tomography angiography revealed that the right internal cerebral vein (ICV) and the vein of Galen had shifted to the right side, and the left ICV passed through the tumor [Figure 1c-f]. The margin between the tumor and the left thalamus (pulvinar) was unclear on MRI. These findings suggested that the tumor arose from the left side within the pineal gland or the left pulvinar thalami. Initial surgery was performed using the left occipital transtentorial approach (OTA) to preserve the ICVs. The lower half of the left side of the tumor was removed [Figure 2a and b].

Based on the 2007 WHO classification, the tumor was classified as a malignant pineal parenchymal tumor or malignant glioma at our hospital and was diagnosed as a malignant glioma through a central review. Subclassification was difficult because of chemotherapy-induced tissue degeneration.

During the central review, postoperative therapy was initiated with whole-brain irradiation (26 Gy, 2 Gy/fraction) and switched to local irradiation (34 Gy) concomitant with temozolomide (TMZ). However, post treatment MRI revealed tumor regrowth (maximum diameter, 47 mm) [Figure 2c and d], and surgical removal was again performed using bilateral OTA. The tumor firmly adhered to the bilateral ICVs and was maximally removed, except for these parts. Postoperative MRI showed a removal rate of 90% [Figure 2e and f]. The patient was discharged 2 weeks after the second surgery without any complications.

One month after discharge, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) revealed high glucose metabolism in the residual tumor [Figure 3a], suggesting high tumor activity. Since a total local dose of up to 80–100 Gy was considered a possible option for local control,[14] additional stereotactic irradiation (gross target volume, 14.19 mm3; planning target volume, 17.01 mm3; central dose, 30 Gy; margin dose, 27 Gy; and six fractions) was performed using Novalis® (Brainlab Co., Japan). The equivalent total dose in 2 Gy/fraction to the tumor site reached 97.5 Gy. Maintenance
Ono, et al.: Long-term survival in pineal diffuse midline glioma

Surgical Neurology International • 2021 • 12(612) | 3

Chemotherapy was continued for 2 years with bevacizumab (Bev) along with TMZ.

MRI performed 2 months after the end of chemotherapy (29 months after the first surgery) again revealed an enlargement in the enhanced area [Figure 3b]. FDG-PET and 11C-methionine (Met) PET [Figure 3c] did not show any accumulation. Tumor recurrence, radiation necrosis, or combination of both were considered possible. Since radical resection was difficult, Bev monotherapy was chosen; Bev effectively decreased the enhanced lesion. Six years after the initial treatment, the tumor size remained stable [Figure 3d], and the patient has not encountered any problem in his student life.

Pathological review

Written informed consent for molecular analyzes and publication was obtained. The sample from the first surgical removal was histologically investigated according to the 2021 WHO classification. Hematoxylin-eosin staining [Figure 4a] revealed marked proliferation of astrocytic tumor cells with nuclear atypia. Immunohistochemical staining was positive for H3.3 K27M [Figure 4b] and negative for H3 K27me3 [Figure 4c]. The Ki67 index was 37%.

The mutations of IDH1/2, H3.3 encoded by H3F3A, and BRAF were screened by the high-resolution melting (HRM) analysis and confirmed by Sanger sequencing. The promoter methylation status of O6-methylguanine-DNA-
methyltransferase ($\text{MGMT}$) was analyzed by a methylation-sensitive HRM (MSHRM) analysis.\[2\] In the HRM analysis, $\text{IDH1/2}$ and $\text{BRAF}$ were wildtypes, but the mutation of $\text{H3F3A}$ was indicated. Sanger sequencing revealed K27M mutation in $\text{H3F3A}$ (c.83A>T) [Figure 4d], and the $\text{MGMT}$ gene promoter was unmethylated [Figure 4e]. Finally, the patient was diagnosed with DMG, the WHO Grade 4.

**DISCUSSION**

We report a case of DMG in the pineal region with a long-term survival of 6 years after multimodal treatment. To date, five cases of pineal DMG have been reported [Table 1].\[5,7,9,11,16\] The origin of the tumor is not constant, and it is also uncertain whether pineal DMG is of homogeneous tumor lineage; however, it is known that the clinical outcome is poor. Although radiotherapy and TMZ treatment according to the glioblastoma have been performed after biopsy or partial excision, no cases of survival ≥2 years have been reported.

Most DMGs do not have methylation in the $\text{MGMT}$ gene promoter, and TMZ has poor treatment efficacy.\[4,11\] In addition, the H3.3 K27M mutation is associated with poor responsiveness to radiotherapy,\[3\] which may also cause poor outcomes of DMG. Consistent with these characteristics of DMG, the present case had unmethylated $\text{MGMT}$ gene promoter and H3.3 K27M mutation, and the expression of H3 K27me3 was reduced. These molecular characteristics may explain the poor responsiveness to ordinal radiochemotherapy.

In the present case, 90% of the tumor was removed through two operations. According to the previous reports, a tumor removal of 78% or more contributes to better prognosis in patients with malignant gliomas.\[15\] Since DMG commonly occurs in difficult-to-operate areas, such as the pons, spinal cord, and thalamus, no reports have clarified the effectiveness of DMG excision. However, for pineal region tumors, maximum resection by OTA may be possible as in the present case. Bilateral OTA has been recommended for tumors with a maximum diameter of >40 mm and those extending to the contralateral side.\[13\]

Another feature in this case was high-dose radiation therapy with a total dose of 97.5 Gy. In general, local irradiation with a total dose of 60 Gy is recommended for glioblastoma. Similar treatment has been applied for DMG in the pineal region previously; however, the clinical outcome has been unsatisfactory.\[5,7,9\] In the present case, the residual tumor even after conventional radiochemotherapy demonstrated high tumor activity, and additional stereotactic radiotherapy was performed. Although the evidence is insufficient, stereotactic radiotherapy is a possible treatment option for local glioblastoma recurrence.\[14\]

The high-dose radiation therapy carries the risk of late complications, including leukoencephalopathy, cerebral atrophy, and radiation necrosis.\[12,18\] Bev has been suggested to have protective effects against radiation necrosis-related adverse events.\[6,8\] Considering the FDG and Met-PET findings\[17\] and treatment responsiveness to Bev therapy in the present case,\[6,8\] the residual enhancing lesion after maintenance chemotherapy could have been radiation necrosis. Even 6 years after the treatment, no obvious leukoencephalopathy or cerebral atrophy was observed; however, further follow-up is necessary because these complications may occur 10 years or more after initial treatment.\[18\] Although the multimodal therapy in the present case was effective, careful decision should be needed as to whether it can be applied to all pineal DMGs.
CONCLUSION

We report a patient with DMG in the pineal region who had a long-term survival of more than 6 years. Maximum resection through bilateral OTA and high-dose radiotherapy followed by Bev might have contributed to the outcome of the present case.

Acknowledgments

The authors would like to sincerely thank Dr. Yoichi Nakazato, professor emeritus at the Department of Pathology, Gunma University Graduate School of Medicine, for conducting the central pathological diagnosis.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Adachi JI, Mishima K, Suzuki T, Fujimaki T, Nishikawa R. Rapid IDH1 gene mutation analysis for intraoperative pathological diagnosis. Neuro Oncol 2014;16 Suppl 3:iii47.
2. Adachi J, Mishima K, Wakiya K, Suzuki T, Fukuoka K, Yanagisawa T, et al. O⁶-methylguanine-DNA methyltransferase promoter methylation in 45 primary central nervous system lymphomas: Quantitative assessment of methylation and response to temozolomide treatment. J Neurooncol 2012;107:147-53.
3. Castel D, Philippe C, Calmon R, Le Dret L, Truffaux N, Boddaert N, et al. Histone H3F3A and HIST1H3B K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes. Acta Neuropathol 2015;130:815-27.
4. Cohen KJ, Heideman RL, Zhou T, Holmes EJ, Lavey RS, Boufet E, et al. Temozolomide in the treatment of children with newly diagnosed diffuse intrinsic pontine gliomas: A report from the children’s oncology group. Neuro Oncol 2011;13:410-6.
5. D’Amico RS, Zanazzi G, Wu P, Canoll P, Bruce JN. Pineal region glioblastomas display features of diffuse midline and non-midline gliomas. J Neurooncol 2018;140:63-73.
6. Furuse M, Nonoguchi N, Kuroiwa T, Miyamoto S, Arakawa Y, Shinoda J, et al. A prospective, multicentre, single-arm clinical trial of bevacizumab for patients with surgically untreatable, symptomatic brain radiation necrosis. Neurooncol Pract 2016;3:272-80.
Ono, et al.: Long-term survival in pineal diffuse midline glioma

7. Gilbert AR, Zaky W, Gokden M, Fuller CE, Ocal E, Leeds NE, et al. Extending the neuroanatomic territory of diffuse midline glioma, K27M mutant: Pineal region origin. Pediatr Neurosurg 2018;53:59-63.
8. Levin VA, Bidault L, Hou P, Kumar AJ, Wefel JS, Bekele BN, et al. Randomized double-blind placebo-controlled trial of bevazucizumab therapy for radiation necrosis of the central nervous system. Int J Radiat Oncol Biol Phys 2011;79:1487-95.
9. Lim JX, Leong A, Tan AR, Tan CL, Nga VD. H3K27M-mutant diffuse midline glioma presenting as synchronous lesions involving pineal and suprasellar region: A case report and literature review. J Clin Neurosci 2020;81:144-8.
10. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: A summary. Neuro Oncol 2021;23:1231-51.
11. Meyronet D, Esteban-Mader M, Bonnet C, Joly MO, Uro-Coste E, Amiel-Benouaich A, et al. Characteristics of H3 K27M-mutant gliomas in adults. Neuro Oncol 2017;19:1127-34.
12. Murphy ES, Xie H, Merchant TE, Yu JS, Chao ST, Suh JH. Review of cranial radiotherapy-induced vasculopathy. J Neurooncol 2015;122:421-9.
13. Qiu B, Wang Y, Ou S, Guo Z, Wang Y. The unilateral occipital transtentorial approach for pineal region meningiomas: A report of 15 cases. Int J Neurosci 2014;124:741-7.
14. Romanelli P, Conti A, Pontoriero A, Ricciardi GK, Tomasello F, de Renzis C, et al. Role of stereotactic radiosurgery and fractionated stereotactic radiotherapy for the treatment of recurrent glioblastoma multiforme. Neurosurg Focus 2009;27:E8.
15. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 2011;115:3-8.
16. Solomon DA, Wood MD, Tihan T, Bollen AW, Gupta N, Phillips JJ, et al. Diffuse midline gliomas with histone H3-K27M mutation: A series of 47 cases assessing the spectrum of morphologic variation and associated genetic alterations. Brain Pathol 2016;26:569-80.
17. Takenaka S, Asano Y, Shinoda J, Nomura Y, Yonezawa S, Miwa K, et al. Comparison of (11)C-methionine, (11)C-choline, and (18)F-fluorodeoxyglucose-PET for distinguishing glioma recurrence from radiation necrosis. Neurol Med Chir (Tokyo) 2014;54:280-9.
18. Tanaka M, Ino Y, Nakagawa K, Tago M, Todo T. High-dose conformal radiotherapy for supratentorial malignant glioma: A historical comparison. Lancet Oncol 2005;6:953-60.
19. van Zanten SE, Baugh J, Chaney B, de Jongh D, Aliaga ES, Barkhof F, et al. Development of the SIOPE DIPG network, registry and imaging repository: A collaborative effort to optimize research into a rare and lethal disease. J Neuro Oncol 2017;132:255-66.

How to cite this article: Ono T, Kuwashige H, Adachi JJ, Takahashi M, Oda M, Kumabe T, et al. Long-term survival of a patient with diffuse midline glioma in the pineal region: A case report and literature review. Surg Neurol Int 2021;12:612.