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Case Report

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

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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.[10] The effect of radiotherapy is limited; there is no established chemotherapy, and the 2-year survival rate is <10%.[19] Five cases of DMG in the pineal region have been reported, with no cases of survival for more than 2 years.[5,7,9,11,16]

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.

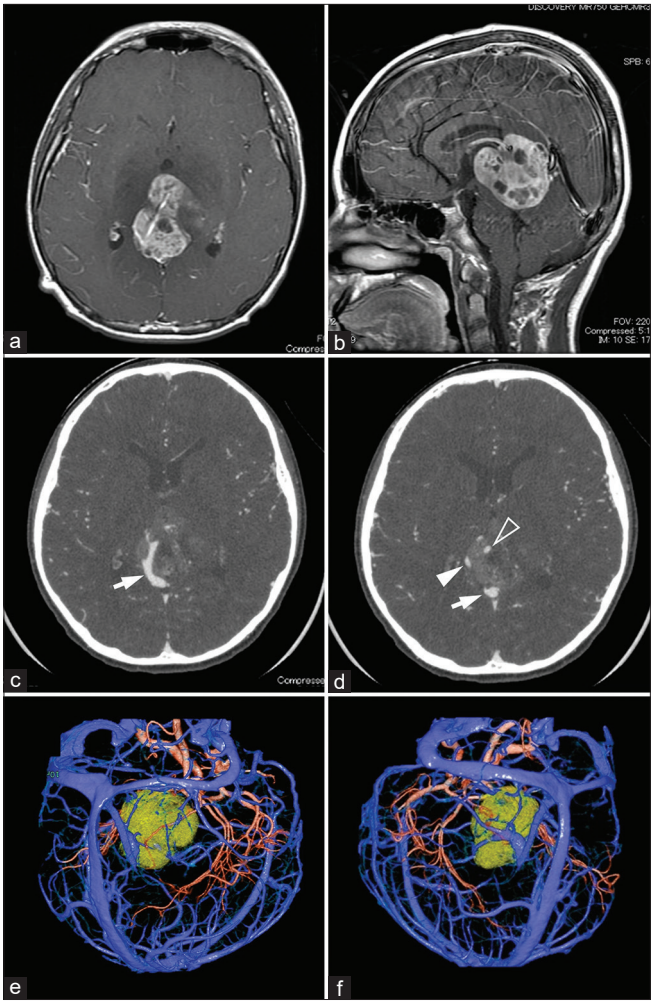

Figure 1: (a and b) Axial and sagittal post contrast T1-weighted images. A pineal region tumor had grown after combination chemotherapy using carboplatin and etoposide, with a maximum diameter of 46 mm. (c and d) Axial source images of preoperative three-dimensional computed tomography angiography (3D-CTA). Arrows (c) and a solid, open arrowhead (d) show the vein of Galen and the right and left internal cerebral vein, respectively; the left internal cerebral vein is passing through the tumor. (e and f) Reconstructed 3D-CTA images for preoperative planning indicate the left (e) and right (f) occipital transtentorial approaches, respectively.

One month after discharge, ^{18}F-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 mm^3; planning target volume, 17.01 mm^3; 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

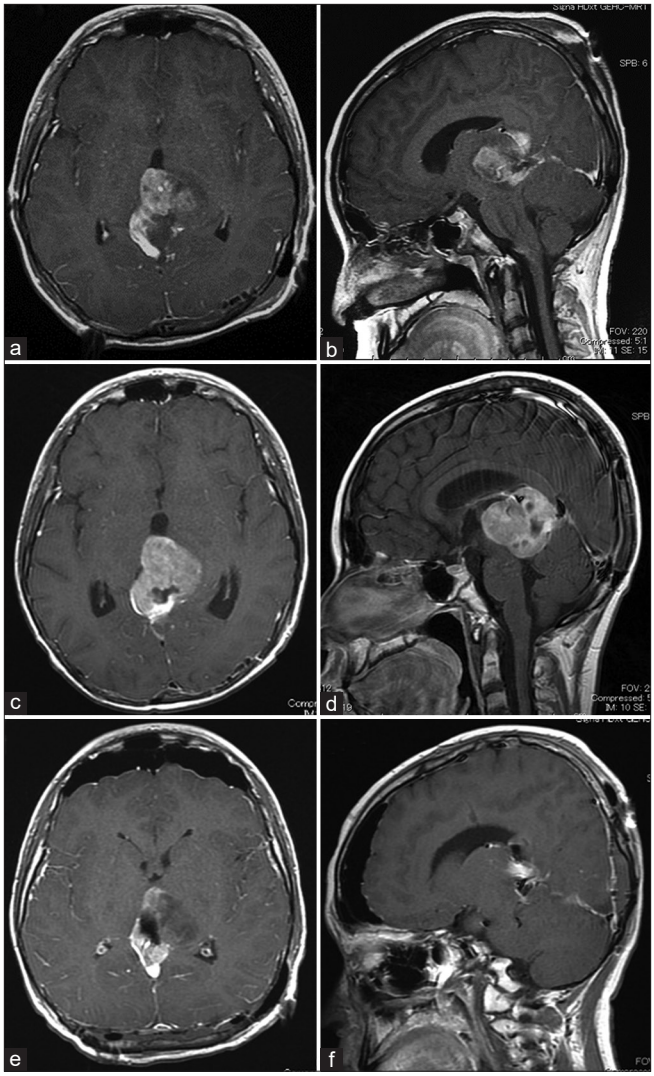

Figure 2: Axial and sagittal post contrast T1-weighted images. (a and b) The tumor was partially removed in the initial surgery by the left occipital transtentorial approach. (c and d) After surgery, whole-brain radiotherapy (26 Gy) and local radiotherapy (34 Gy) were performed concomitantly with temozolomide administration; however, the residual tumor enlarged. (e and f) Subsequently, the second surgery was performed using bilateral occipital transtentorial approach, and approximately 90% of the tumor volume was removed.

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 ^{11}C-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

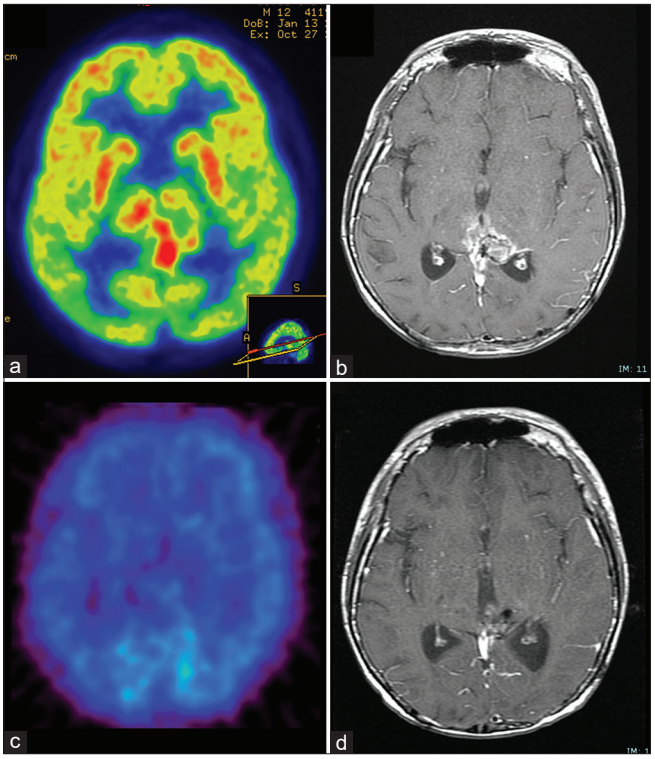

Figure 3: (a) ^{18}F-fluorodeoxyglucose positron emission tomography 6 weeks after the second surgery showing high glucose metabolism in the residual tumor. (b) Post contrast T1-weighted images obtained 2 months after the end of maintenance chemotherapy (29 months after initial surgery) showing enlargement of the enhancing lesion. (c) However, ^{11}C-methionine positron emission tomography demonstrated no abnormal metabolism. (d) Post contrast T1-weighted images reveals no recurrence under bevacizumab monotherapy 6 years after initial surgery.

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[1] and confirmed by Sanger sequencing. The promoter methylation status of O^6-methylguanine-DNA-

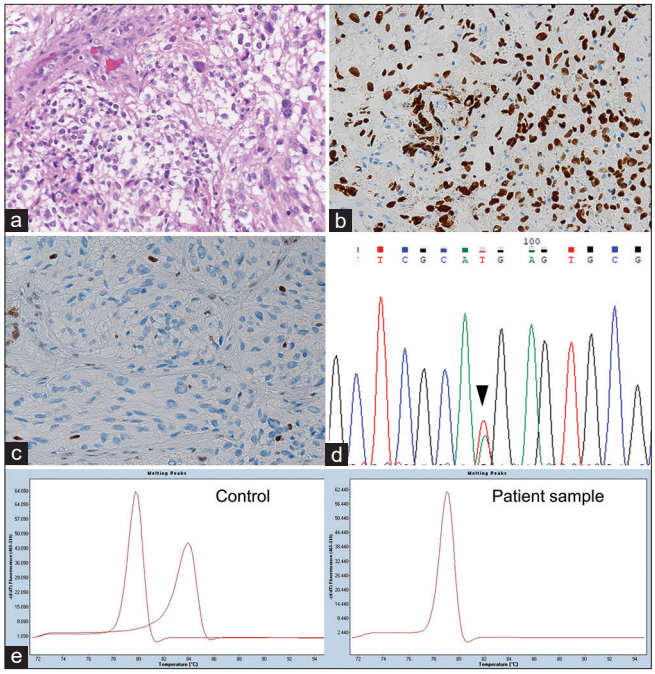

Figure 4: Pathological and molecular findings of the present tumor. (a) Hematoxylin and eosin staining showing marked diffuse proliferation of the atypical astrocytic tumor cells. (b and c) Immunohistochemical staining showing that the tumor cells were positive for H3.3 K27M and negative for H3 K27me3. (d) Sequencing chromatogram, obtained using Sanger sequencing, showing K27M mutation in H3F3A (c. 83A>T) (arrowhead). (e) *MGMT* methylation-sensitive high-resolution melting (MSHRM) analysis showing two peaks of 0% (left) and 100% (right) methylated controls in the left panel. Two different peaks are obtained for the PCR product derived from the unmethylated and methylated templates. The right panel is from the sample of the present case demonstrating a peak of unmethylated DNA. Data were analyzed using the Tm Calling software module.

methyltransferase (*MGMT*) was analyzed by a methylation-sensitive HRM (MSHRM) analysis.[2] In the HRM analysis, *IDH1/2* and *BRAF* were wildtypes, but the mutation of *H3F3A* was indicated. Sanger sequencing revealed K27M mutation in *H3F3A* (c.83A>T) [Figure 4d], and the *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 *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 *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.

Table 1: Summary of the clinical information of diffuse midline glioma in the pineal region, H3 K27M-mutant.

Authors (year)	Age/Sex	Tumor Origin	Surgery (rate)	RT (dose)	ChT	OS (Mo)	Outcome	Remarks
Solomon *et al.* (2016)[16]	65/M	NA	Biopsy	NA	NA	NA	NA	
Meyronet *et al.* (2017)[11]	21/F	NA	Biopsy	None	None	3	Died	
D'Amico *et al.* (2018)[5]	38/M	Pineal gland or thalamus	Biopsy, PR (65–75%)	CRT (60Gy)	TMZ	23	Died	
Gilbert *et al.* (2018)[7]	12/F	Pineal gland	Biopsy, later resection (NA)	CRT (NA)	TMZ, clinical trial (metronomic cyclophosphamide, temsirolimus)	NA	NA	Spinal dissemination after chemotherapy
Lim *et al.* (2020)[9]	22/F	Multicentric (pineal and suprasellar resions)	Biopsy	CRT (60Gy)	TMZ	7	Alive	
Present Case	12/M	Pineal gland or thalamus	Two-stage surgery (90%)	WBRT (26Gy) CRT (34Gy) SRT (30Gy, 6fr)	TMZ, Bev	72	Alive	

Bev: Bevacizumab, ChT: Chemotherapy, CRT: Conventional radiotherapy, F: Female, fr: Fractionated, M: Male, Mo: Months, NA: Not available, OS: Overall survival, RT: Radiotherapy: SRT: Stereotactic radiotherapy, STR: Subtotal resection, TMZ: Temozolomide, WBRT: Whole brain radiotherapy

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.

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Declaration of patient consent

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

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Nil.

Conflicts of interest

There are no conflicts of interest.

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