

# Personalized combination therapy for diffuse midline glioma: A case report

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Received November 11, 2024; Accepted February 6, 2025

DOI: 10.3892/ol.2025.14980

**Abstract.** The present study aimed to analyze the efficacy of personalized combination therapy for patients with H3K27M mutant diffuse midline glioma (DMG) so as to explore new treatment options for further clinical research. The clinical data and prognosis of a patient with H3K27M mutant DMG are summarized and discussed in the context of the relevant literature. The patient was a 20-year-old female diagnosed with DMG treated with a combination of surgery, radiotherapy, chemotherapy, electric field therapy, immunotherapy and targeted therapy. An overall survival time of 28 months was achieved. In summary, personalized treatment strategies are expected to provide longer-lasting survival benefits for patients with DMG.

## Introduction

Diffuse midline gliomas (DMG) with the H3K27M mutation are primary malignant tumors located in the linear structures of the brain; according to the CBTRUS statistical report, DMG is rare in adults, with an annual incidence rate of ~0.1 cases per 1 million people, accounting for 2-3% of all gliomas in adults. H3K27M mutation is a core molecular hallmark of DMG, and >70% of patients with DMGs carry this mutation. The prognosis for this disease is extremely poor, and the mortality rate is extremely high, with a median overall survival of only 12 months for newly diagnosed patients and a 5-year survival rate of only 1% (1). Other molecular types of DMG include the EZHIP overexpression type, EGFR mutant type and H3G34 mutant type. In addition to use of conventional surgery, radiotherapy and chemotherapy, the exploration of new approaches

is essential to improve patient prognosis. Currently, there are few reports on the diagnosis and treatment of H3K27M mutant diffuse midline glioma (2). In the present study, a patient with adult H3 K27M mutant diffuse midline glioma was admitted to the Department of Radiotherapy of Oncology, Shenzhen People's Hospital (Shenzhen, China) and was administered a combination of treatment strategies such as surgery, radiotherapy, chemotherapy, electric field therapy, immunotherapy and targeted therapy, which is a new innovative direction for treatment.

## Case report

A 20-year-old woman presented to Shenzhen People's Hospital in September 2021 with a deviated angle of the mouth and left-sided limb dysfunction. Subsequently, a magnetic resonance imaging (MRI) examination was performed at the Imaging Department of Shenzhen People's Hospital (Shenzhen, China), which showed bilateral thalamic masses (Fig. 1). The thalamus assists in maintaining consciousness and perceptual functions. Surgical procedures can damage the structures of the thalamus, leading to complications such as impaired memory, language or motor function, and the high risk of surgery requires extra care in the surgeon's evaluation. On the recommendation of the surgeon, the patient underwent microscopic resection of the right thalamic mass. Postoperative pathology showed a DMG of the right thalamus, with H3K27M mutation, at World Health Organization (WHO) grade 4 (3). The immunohistochemistry protocol was as follows: Paraffin-embedded tissue sections were deparaffinized and hydrated sequentially in xylene, anhydrous ethanol, gradient ethanol and distilled water. The sections were then placed in EDTA antigen repair buffer, heated at 95-100°C for 20 min, cooled for 10 min and rinsed three times (3 min/wash) with PBS. Next, 3% peroxidase blocker was added at 36°C for 10 min, and the sections were rinsed three times with PBS (3 min/wash). Primary antibodies were added to the sections and incubated at 4°C overnight (12 h). Sections were then preheated at 37°C for 30 min and washed three times (5 min/wash) with PBS (cat. no. 950-300; Roche Diagnostics). A secondary antibody (horseradish peroxidase-conjugated; 1:100; cat. no. 760-500; Roche Diagnostics) was added and incubated in an oven at 37°C for 8 min, then washed three times (5 min/wash) with PBS. After removing the PBS solution, freshly prepared DAB

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**Key words:** diffuse midline glioma, H3K27M mutation, comprehensive treatment, long-term survival

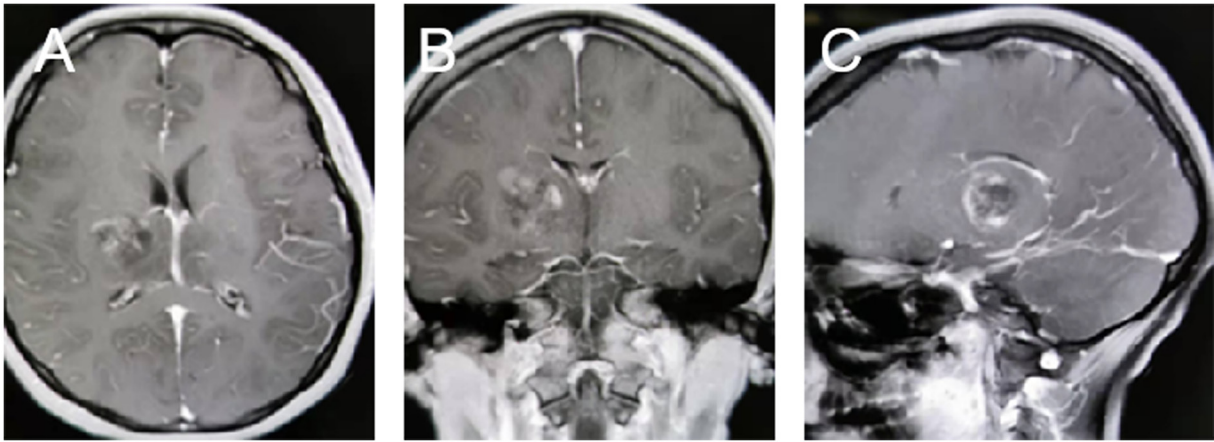


Figure 1. Head magnetic resonance imaging. (A) Magnetic resonance cross-section showing compression of the ventricles by the tumor, resulting in midline shift. Magnetic resonance (B) coronal position and (C) sagittal plane images showing masses invading the thalamus that are poorly demarcated from the surrounding tissue.

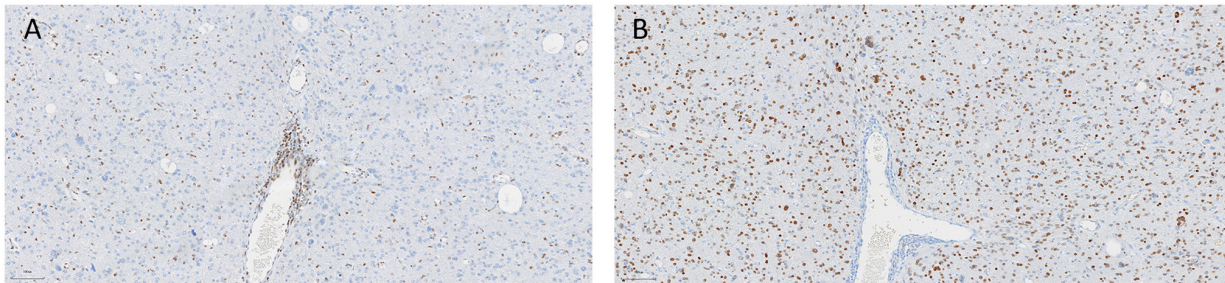


Figure 2. Immunohistochemistry results. (A) Immunohistochemically, a lack of immunoreactivity for H3K27me3 can be observed. (B) H3K27M expression is positive (original magnification, x200).

color development solution was added and incubated for 3-5 min. After rinsing with tap water, the sections were incubated with hematoxylin stain for 10 to 30 sec, and then rinsed with PBS. Finally, the sections were dehydrated, cleared and sealed. Light microscopic examination (Leica Biosystems) demonstrated the following results: H3K27M(+) (1:100; cat. no. ZA-0321), H3K27me3(-) (1:100; cat. no. ZA-0327), isocitrate dehydrogenase 1 (IDH1)(-) (1:50; cat. no. TW-0821), glial fibrillary acidic protein(+) (1:1,000; cat. no. MX-047), p53(-) (1:100; cat. no. BPM6168), oligodendrocyte transcription factor-2(+) (1:100; cat. no. EP-112), Ki-67(+)(50%) (1:100; cat. no. BP-6045), transcriptional regulator ATRX(+) (1:200; cat. no. MX-071) (all Roche Diagnostics). O6 methylguanine DNA methyltransferase (MGMT) promoter methylation negativity (cat. no. MX-0361), and a lack of 1p/19q co-deletion (Figs. 2 and 3). At 1-month post-surgery, head MRI follow-up showed a thalamic glioma on the left side and postoperative changes on the right side of the lesion; Magnetic resonance spectroscopy (MRS) showed that MRS changes in the left thalamic lesion were consistent with the tumor lesion, and MRS around the right thalamic surgical area did not show any significant abnormality (Fig. 4).

As the tumor could not be completely removed by surgery, the patient started postoperative adjuvant radiotherapy in November 2021, following the Radiation Therapy Oncology Group principles of radiotherapy target delineation for high-grade gliomas (4). The prescribed dose for the first phase

was 46 Gy/23 fractions and the prescribed dose for the second phase of treatment was 14 Gy/7 fraction. During radiotherapy, concurrent temozolomide chemotherapy (75 mg/m<sup>2</sup>, orally, after 4 h of fasting, once a day) was administered. At 4 weeks post-synchronous radiotherapy and chemotherapy, the patient entered the adjuvant chemotherapy stage and orally took 150-200 mg/m<sup>2</sup> temozolomide daily for 5 consecutive days, repeating every 28 days for a total of 12 cycles. Notably, the treatment was combined with maintenance with tumor-treating fields (TTFields) during and after radiotherapy.

During the follow-up period, the patient underwent a brain-enhanced MRI follow-up assessment every 3 months, and the efficacy was analyzed according to the Response Assessment Criteria in Neuro-Oncology (RANO) (5). As of June 2023, the patient developed the symptom of unsteady walking, and the follow-up cranial MRI showed significant changes in the long T1 and long T2 abnormal signals in the bilateral thalamus, bilateral cerebellar hemispheres and cerebral pons (Fig. 5). Tumor progression was considered after a multidisciplinary discussion based on RANO criteria.

In August 2023, the patient was started on maintenance therapy with bevacizumab (5 mg/kg once every 2 weeks) in combination with TTFields. After 2 months, follow-up brain enhancement MRI showed a slightly larger intracranial space-occupying lesion than before (in June 2023, the size of the lesion in the thalamus was 20x17 mm, and the size of the lesion in the cerebellar hemispheres and pontine brain

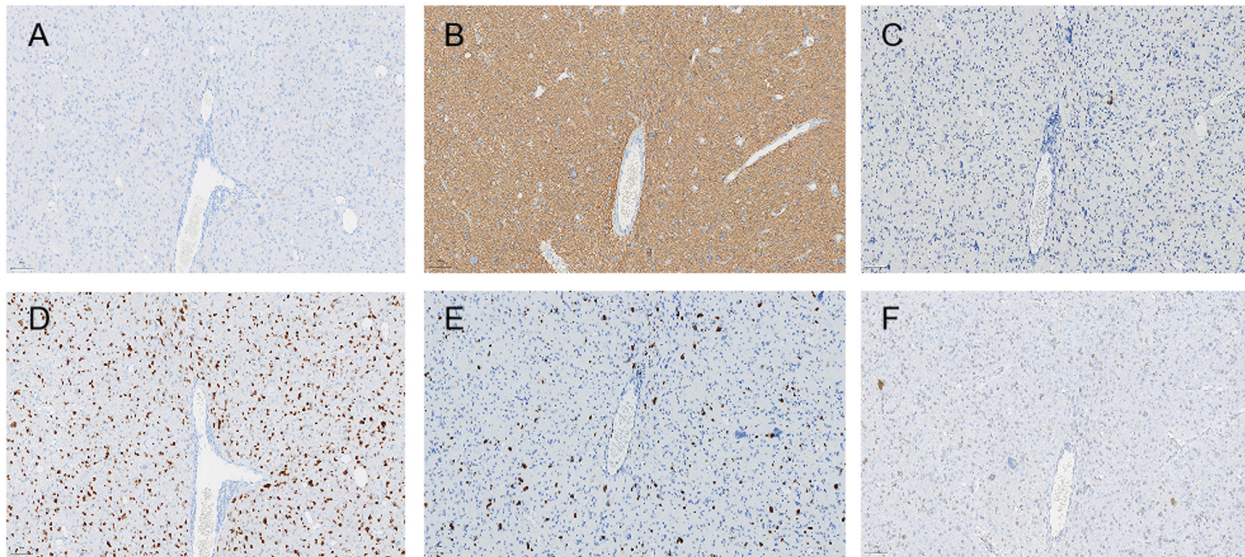


Figure 3. Differential diagnosis of diffuse midline glioma. Immunohistochemical staining results showing the specimen to be (A) isocitrate dehydrogenase 1(-), (B) glial fibrillary acidic protein(+), (C) p53(-), (D) oligodendrocyte transcription factor-2(+), (E) Ki-67(+) and (F) transcriptional regulator ATRX(+) (original magnification, x200).

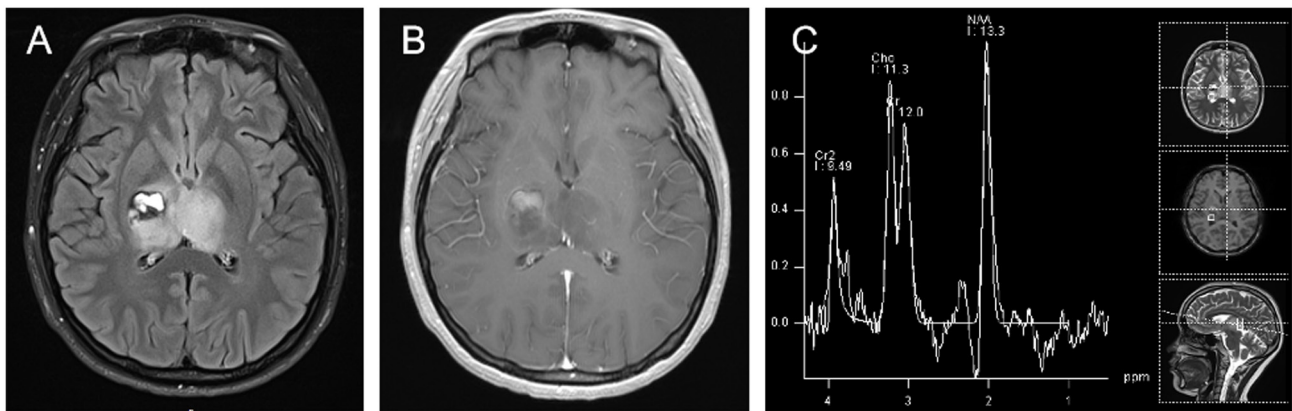


Figure 4. Head magnetic resonance imaging (1 month postoperatively, November 2021). (A and B) Partial resection of the right-hand side lesion, with residual thalamic glioma on the left side. (C) A markedly elevated peak in choline, a slight decrease in creatine and an N-acetyl aspartate/creatine ratio of <1.5 indicating a residual tumor. Cho, choline; Cr, creatine; NAA, N-acetyl aspartate.

was 28x21 mm; in October 2023, the size of the lesion in the thalamus was 30x20 mm, and the size of the lesion in the cerebellar hemispheres and pons was 28x25 mm), indicating that the patient's disease was poorly controlled. In October 2023, the treatment regimen was changed to bevacizumab (10 mg/kg every 2 weeks) and pembrolizumab (200 mg every 3 weeks) immunotherapy in combination with TTFields. In December 2023, follow-up brain-enhanced MRI showed slow progression of the lesion. The efficacy was assessed as stable disease (SD) according to the RANO criteria. However, the patient's family wanted to achieve more effective tumor suppression, so they purchased their own targeted drugs, ONC201 (510 mg orally once a week) and ONC206 (60 mg orally once a week) (both Lindburg Pharmacy, Inc.), which are not currently indicated for use in China, and used them for personalized combination therapy with bevacizumab, pembrolizumab and TTFields in December 2023. In January 2024, a follow-up cranial MRI showed that the bilateral thalamus, dorsal pontine, cerebellar

vermis and bilateral cerebellar hemispheric lesions had not changed, showing temporary control of the lesion.

In February 2024, due to aspiration pneumonia, the patient suspended the treatment of bevacizumab and pembrolizumab but still insisted on the treatment using TTFields, ONC201 and ONC206. In March 2024, the patient developed symptoms of choking on drinking water, difficulty in swallowing and weakness while coughing up sputum. In March 2024, a follow-up cranial MRI showed that the foci of the bilateral thalamus, dorsal pontine, cerebellar earth and bilateral cerebellar hemispheres had increased in size (Fig. 6) compared with the previous measurements (the size of the lesion in the thalamus was 30x20 mm, and the size of the lesion in the cerebellar hemispheres and pons was 33x29 mm), and tumor progression was considered. The patient subsequently received respiratory treatment for a lung infection, and anti-tumor therapy was suspended. The patient succumbed to respiratory failure in March 2024.

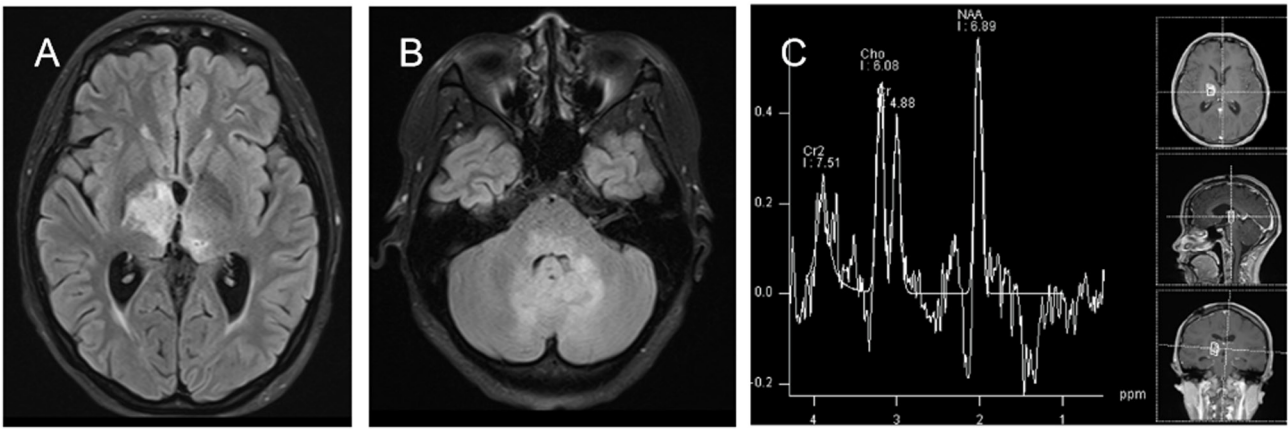


Figure 5. Head magnetic resonance imaging (August 2023). (A and B) Abnormal changes in long T1 and long T2 signals in both the thalamus and cerebellum. (C) Magnetic resonance spectroscopy (MRS) revealed a marked elevation of the choline peak and a modest reduction in creatine levels. Furthermore, the N-acetyl aspartate-to-creatine (NAA/Cr) ratio was observed to be  $< 1.5$ , suggesting the persistence of residual tumor tissue within both cerebellar hemispheres and the pons.

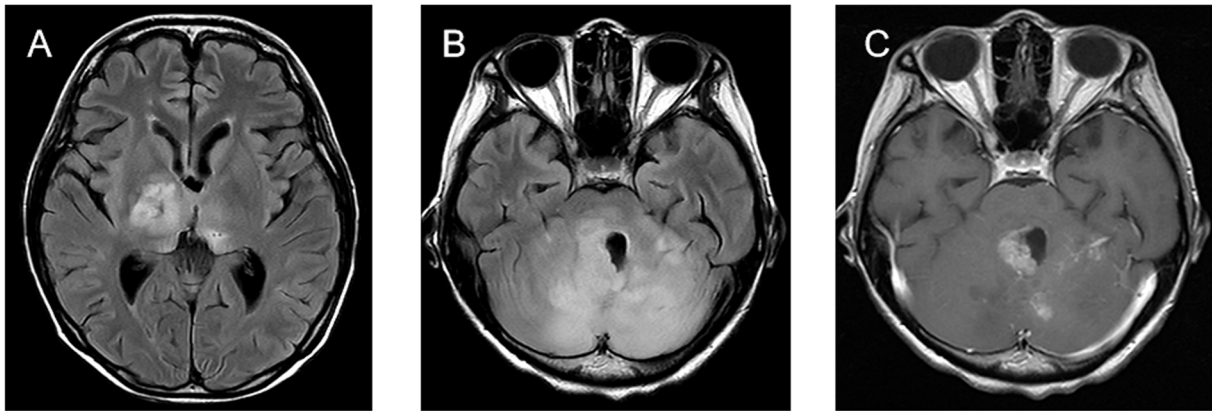


Figure 6. Head magnetic resonance imaging (February 2024). Images captured at (A) the level of the bilateral thalamic brain structure, (B) at the level of the dorsal pontine brain structure and (C) at the level of the cerebellar bulbs brain structure. Multiple areas of oedema are seen, indicating that the tumour is progressing.

## Discussion

H3K27M mutant glioma is a relatively newly discovered disease. This mutation was first reported in 2012 and typically occurs in H3.1 or H3.3 subtypes, serving as the initiating mutation in tumors (6). This mutation coexists with multiple genetic changes, but does not coexist with IDH and EGFR mutations. H3K27M mutant tumors usually have unmethylated MGMT, leading to poor efficacy of temozolomide in radiotherapy. This mutation also leads to H3K27 trimethylation loss and H3K27 acetylation increase, affecting gene expression. In 2016, the WHO classified H3K27M mutant tumors as a unique form of grade IV glioma. The updated 2021 classification has been further refined to include prognostically relevant molecular annotation for H3K27 (3,7). The H3K27M mutation is associated with poor survival rates, and affects children and young adults. Up to 90% of cases in pediatric diffuse intrinsic pontine glioma (DIPG) carry this mutation, and 15-60% of cases in adult DMG also have this mutation (8).

Radiotherapy is currently the only standard of care that temporarily relieves the symptoms of DMG, delays disease

progression and prolongs median survival time (9); however, there is still insufficient evidence to determine the optimal radiotherapy target area and dose. In 2017, the Chinese consensus of experts on radiotherapy for gliomas recommended a total radiation dose of 45-54 Gy (1.8-2.0 Gy/dose). Depending on the specific circumstances (such as high malignancy), 54-60 Gy (1.8 to 2.0 Gy/dose) or 39 Gy (3.0 Gy/dose) could also be selected (10). The Korean Society of Neuro-Oncology guideline 2021.1 for adult DMGs recommends a total dose of 54 to 60 Gy, and the therapeutic target range includes 1-2 cm of tumor outgrowth for conventional segmental irradiation (11). In the present case, the patient's tumor was located in the bilateral thalamus and the tumor could not be entirely removed by surgery. Postoperative radiotherapy was the primary treatment method. Therefore, the radiotherapy plan was developed according to the RTOG high-grade glioma radiotherapy target area delineation method (4). The total dose of radiotherapy was up to 60 Gy, and the patient's whole radiotherapy process went smoothly without any prominent radiotherapy toxicities or side effects. It is well known that the high expression of MGMT in DMG with H3K27M mutation can lead to resistance

to temozolomide in patients (12,13). In addition, the presence of the blood-brain barrier limits the entry of most antitumor drugs into the brain (14,15). However, a retrospective study using radiotherapy with synchronized temozolomide followed by adjuvant temozolomide chemotherapy for the treatment of DMGs in children showed that the median time to progression after treatment was 10.2 months. The 1-year progression-free survival (PFS) rate was 41.7%, with a median survival time of 13.5 months, suggesting that chemotherapy improves outcomes (16). In the present case, the patient was treated postoperatively with radiotherapy synchronized with temozolomide chemotherapy followed by a sequential 12-cycle long course of temozolomide adjuvant chemotherapy, and the patient's disease did not progress throughout the entire course of chemotherapy. Therefore, whether the combination of radiotherapy and chemotherapy would have a long-term survival effect still requires further study.

Tumor-treating fields (TTFields) is a portable, non-invasive anticancer therapy whose primary antitumor mechanism of action is the use of alternating electric fields to selectively inhibit the mitosis of tumor cells, thus achieving the purpose of tumor control. Currently, TTFields is mainly approved for the treatment of glioblastoma. In the international EF-14 trial, the median overall survival (OS) time of the combined treatment group of electric field therapy + radiotherapy was 20.5 months, while that of the control group was 15.6 months (17). However, there needs to be more large clinical studies reporting the efficacy of TTFields in the treatment of DMGs, and there have only been case reports of this treatment demonstrating efficacy. In one case, a 3-year-old child with DMG who was treated with TTFields in combination with TMZ after concurrent chemoradiotherapy achieved PFS for 9 months, with gradual improvement over time (18). In the present case, the patient was treated with adjuvant TTFields throughout the postoperative period, and the patient's PFS time reached 21 months, far exceeding that of other studies using radiotherapy alone (16). The treatment also did not add additional toxic severe side effects. Patients with DMG may achieve more significant survival benefits in combination with TTFields based on radiotherapy.

DMGs with H3K27M mutation pose an excellent challenge for complete surgical tumor removal due to their growth in midline locations such as the brainstem. However, in recent years, with the rapid development of targeted therapies and immunotherapies, it has been found that stereotactic biopsies are safe with the ability to obtain enough tissue to generate valuable molecular information, which can help in the research of new antitumor drugs (19). The biopsies are therefore widely used in the clinic. Studies have shown that gliomas have a variety of immunosuppressive factors, including programmed cell death ligand 1 and indoleamine 2,3-dioxygenase, and that elevated levels of these immunosuppressive factors can hinder antigen presentation (20,21). Currently, various immune checkpoint inhibitors are widely used in the treatment of clinical solid tumors and have achieved sound therapeutic effects (20,21). For the application of immune checkpoint inhibitors in DMG, an American single-center clinical trial explored the efficacy of immunotherapy for DIPG after relapse. The results showed that the combination of radiotherapy and immunotherapy or immunotherapy alone prolonged the survival of patients by

at least 14 months compared with no treatment. All treatment was well tolerated, with no acute or late toxic reactions. Thus, clinically, combination immunotherapy is expected to improve patient survival (22).

Combinations of targeted therapies and immunotherapies, among others, for the treatment of DMGs, are also currently being explored with the aim of evaluating whether potential synergistic effects can be exploited to improve the outcome of these highly aggressive tumors. Shandong Cancer Hospital reported that an adult patient with DMG responded to treatment with olaparib in combination with bevacizumab and achieved complete remission with an OS time of 16 months (23). Recently, ONC201 and its analogous compound ONC206, an orally administered small molecule that crosses the blood-brain barrier and enhances the activity of TNF-related apoptosis-inducing ligand to inhibit tumor growth and induce cancer cell death, have also been the subject of intense research (22). In a study published by Venneti *et al* (24), ONC201 demonstrated significant antitumor activity in both non-recurrent and recurrent DMGs, with a median OS time of 21.7 months in patients with non-recurrent tumors and 9.3 months in patients with recurrent tumors. The objective remission rate was 36.8% in patients with non-recurrent tumors and 40.9% in patients with recurrent tumors (24). In the present case, bevacizumab targeted therapy was added after the first disease progression in August 2023, together with maintenance TTFields. The treatment was changed to a bevacizumab combined with pembrolizumab regimen in October 2023 after consideration of the lack of significant efficacy. After the combination therapy resulted in SD, the patient was again administered onc201 and onc206 targeted drugs under the existing combination therapy regimen in December 2023. Imaging again evaluated the patient as exhibiting SD in January 2024, and under the combination therapy strategy of TTFields + targeted therapy + immunotherapy, the patient's PFS time reached 5 months, suggesting that the combination therapy strategy is beneficial in improving the prognosis of patients with DMG.

In conclusion, DMG, a highly aggressive brain tumor with a median survival time of <1 year, poses a major therapeutic challenge for clinicians and researchers. Precision medicine approaches, such as electric field therapy, immunotherapy and targeted therapies, may have great potential to improve the prognosis of patients with this deadly disease. The present patient achieved a long-term survival benefit of >29 months of OS following use of a comprehensive treatment strategy, suggesting that exploiting the potential synergistic effects of multiple treatment modalities may improve the prognosis of this highly aggressive type of tumor. It is hoped that more clinical studies in the future will explore the possibility of finding better solutions to treat this disease.

#### Acknowledgements

Not applicable.

#### Funding

No funding was received.

### Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

### Authors' contributions

LG, ZHL and JZZ treated the patient. LJW and MQS analyzed the data, conducted the histopathological evaluation and assisted in writing the manuscript. LJW and MQS confirm the authenticity of all the raw data. All authors contributed to the article and approved the submitted version.

### Ethics approval and consent to participate

The study was approved by the Ethics Committee of Shenzhen People's Hospital (Shenzhen, China; approval no. LL-KY-2024154-01), and the study complied with the ethical standards set forth in the 1964 Declaration of Helsinki.

### Patient consent for publication

Written informed consent for publication of this case report and any accompanying images was obtained from the relatives of the patient.

### Competing interests

The authors declare that they have no competing interests.

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