



Multiple subtentorial metastasis in diffuse midline glioma receiving tumor treating fields: a case report and literature review

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Abstract: Diffuse midline glioma (DMG) is one of fatal glioblastoma multiforme (GBM) with no proven medical therapies. Tumor treating fields (TTFields) is a new revolutionary therapy for GBM which prolongs the overall survival time obviously. However, we can observe more tumor growth phenomena (such as distant multiple metastases) than before. This report describes an adult patient who presented headache and dizziness, accompanied by left limb weakness, nausea, and vomiting following car accident trauma, following imaging examinations suggested thalamus GBM. He was treated with subtotal excision. Final pathology was diagnosed as DMG with H3F3A mutation, isocitrate dehydrogenase (IDH) wild type. Following concurrent chemoradiation therapy (CCRT) and adjuvant temozolomide (TMZ) chemotherapy + TTFields therapy were carried out. Supratentorial tumor has been exhibited a partial radiological response for nine months until TTFields was used irregularly or even discontinued in the later stage. Especially, subtentorial and spinal multiple metastasis occurred during this time. Both supratentorial and subtentorial tumors were treated with surgery, radiotherapy, chemotherapy, even targeted drugs, with the only difference being TTFields, but we could see different consequences for tumor growth. One conclusion might be drawn that TTFields can provide a longer survival time (14 *vs.* 8 months reported before) for DMG patients and improve survival benefits. However, we can observe that patients maybe die from subtentorial metastasis because TTFields could not cover the subtentorial tumors, which is the focal challenge at present. So further research on subtentorial tumors with TTFields is urgently needed.

Keywords: Diffuse midline glioma (DMG); tumor treating fields (TTFields); subtentorial metastasis; case report

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Introduction

Diffuse midline glioma (DMG) is one of fatal glioblastoma multiforme (GBM) with no standard effective medical therapies. GBM treatment consists of surgery, radiotherapy, and chemotherapy with temozolomide (TMZ) (1). In 2018, the new version of National Comprehensive Cancer Network (NCCN) guidelines clearly indicated

tumor treating fields (TTFields) therapy as a category 1 recommendation (2). As a result, patients can live longer after surgery with 'concurrent chemoradiation therapy (CCRT) and adjuvant TMZ chemotherapy + TTFields therapy'.

Patients can benefit from longer overall survival (OS) with TTFields, which increased from 16 to 20.9 months (3), but some new and rare challenges have emerged, among

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which distant metastasis to the central nervous system (CNS) has been reported only occasionally in the past. This case describes a patient who exhibited a partial radiological response of the supratentorial tumor following initiation of TTFields therapy for 9 months, but showed subtentorial and spinal multiple metastasis 4 months after beginning TTFields treatment. TTFields can provide a longer survival time (14 months) in this case than previous report (8 months) for DMG patients (4). However, patients maybe die from subtentorial metastasis at last because the coverage area of TTFields, which is generally effective for supratentorial tumors, but may not applying to subtentorial tumors.

We present the following article in accordance with the CARE reporting checklist (available at <https://dx.doi.org/10.21037/atm-21-4395>).

Case presentation

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A 28-year-old male patient presented headache and dizziness, accompanied by left limb weakness, nausea, and vomiting following car accident trauma. On the initial physical examination, the left limb strength was grade 4 and hypoesthesia. Without abnormal family and medical history. Subsequently, he underwent imaging examinations, and both skull computerized tomography (CT) and magnetic resonance imaging (MRI) suggested a mass with hemorrhage in the right thalamus (*Figure 1*). The mass was heterogeneous with different composition, as well as irregular necrotic cystic areas with enhancement. The preoperative three-dimensional reconstruction of lesions and surrounding white matter fiber bundles showed that the main functional fiber bundles were pushed to the peripheral and anterior upper parts of the lesions.

Next, the patient underwent a right thalamic tumor resection assisted by ultrasonic navigation and electrophysiological monitoring, and the necrotic and cystic areas of the tumor were removed. The ventricle was opened intraoperatively and an external drainage tube was placed for drainage. The patient was pathologically

diagnosed with GBM (*Figure 2*). Tumor gene analysis showed non-methylation of the O6-methylguanine-DNA methyltransferase (MGMT) promoter, no 1p/19q co-deletion, isocitrate dehydrogenase (IDH) wild type, and human telomerase reverse transcriptase [TERT(-)].

The patient was initially treated with CCRT, which involved initial loading with TMZ concurrently with conformal radiation therapy (60 Gy) followed by monthly TMZ. TTFields was initiated after two cycles of TMZ adjuvant therapy, and the TTFields utilization rate was 83% until 8 months postoperatively. The patient exhibited a partial radiological response according to the 2010 response assessment in neuro-oncology (RANO) standard (*Figure 3*). The patient developed symptoms of lumbago, leg pain, and defecation weakness 9 months after the initial operation. MRI revealed metastatic tumors on the L5 spinal cord. The tumor was found to be surrounding the cauda equina nerve and was completely removed (*Figure 4*).

Postoperative pathological examination reported GBM metastasis, and the tumor gene analysis results were consistent with those of the thalamic tumor (*Figure 5*). In addition, H3F3A mutation was found, which was diagnosed as DMG. H3F3A-mutant DMG is a fatal malignancy with no proven medical therapies. ONC201 is a small molecule selective antagonist of dopamine receptor D2/3 (DRD2/3) with an exceptional safety profile. Following up on a durable response in the first H3F3A-mutant DMG patient who received ONC201 (NCT02525692), an expanded clinical study suggests that 3 adults among the 14 recurrent patients remain on treatment progression-free with a median follow up of 49.6 weeks. Radiographic regressions were reported in a subset of patients with thalamic and pontine gliomas, along with improvements in disease-associated neurological symptoms (5). In addition, CDK6 gene amplification was detected, and it has been reported that GBM cell lines carrying *CDK6* gene amplification were sensitive to palbociclib (6). While palbociclib was only approved by FDA as a potential benefit drug for other cancers.

Subsequently, the patient received local radiation therapy (54 Gy/27 F) in the lumbar tumor region. However, 1 month after the operation, four new metastases were found in the cervical 6 and lumbar 2–4 spinal cord (*Figure 6*), so the cervical spinal metastasis was treated with palliative radiotherapy (46 Gy/23 F). Meanwhile, the patient also received systemic chemotherapy: bevacizumab 600 mg (D1) + palbociclib 125 mg/day (D1–21). However, palbociclib was discontinued because the patients could not tolerate the side effects, especially myelosuppression

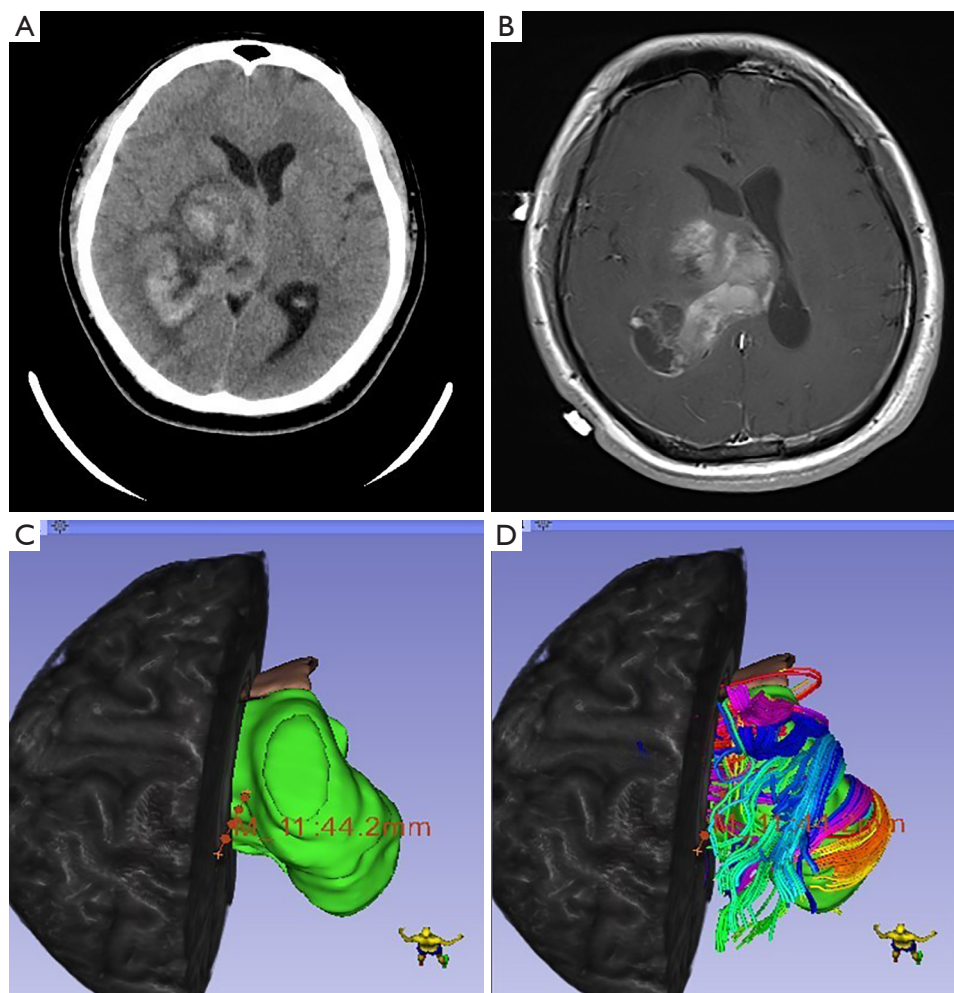


Figure 1 Preoperative imaging and 3D reconstruction. (A) Preoperative CT showing tumor and hemorrhage on the right side of the thalamus. (B) Preoperative MRI T1 with gadolinium contrast showed a typical contrast enhancement pattern of GBM-associated hemorrhage and necrosis. (C,D) 3D Slicer software was used to reconstruct the relationship between the tumor and the ventricle and surrounding white matter tracts, which indicated that important functional fiber bundles encircled the tumor. CT, computed tomography; MRI, magnetic resonance imaging; GBM, glioblastoma multiforme.

and gastrointestinal reactions.

Due to COVID-19, the supply of TTFields accessories has been interrupted, resulting in patients having to discontinuously use TTFields from lumbar metastasis surgery to 1 week prior to radiotherapy, during that time the TTFields utilization rate decreased to 78%. The following month, TTFields had to be terminate due to lack of accessories. MRI showed that the tumor in the right thalamus had developed, and a new metastatic tumor appeared in cerebellopontine angle (*Figure 7*). Two months later, the patient died.

Discussion

The median OS of different genotypes of GBM varies, which has been reported in literature to be between 13.5 and 16.6 months (7). Our patient was classified as IDH wild type, no 1P/19Q co-deletion, and without TERT mutations; the median OS for this type should be >16.6 months. Judging by the imaging changes of the primary thalamic tumor in this patient, the cause of death was not the recurrence and enlargement of the primary thalamic tumor, but the metastatic spread throughout the CNS, especially the brainstem and cervical spinal cord metastases. These may

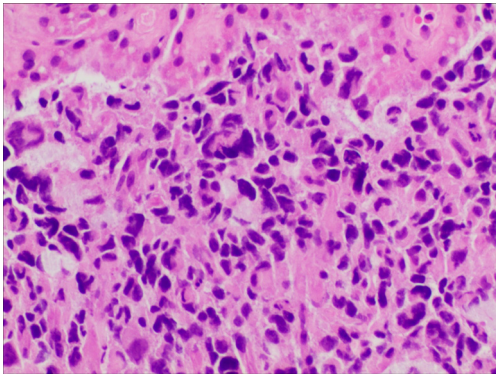


Figure 2 Light micrographs of the glioma. Tissue stained with hematoxylin and eosin (H&E) showing diffuse and densely distributed tumor cells. Nuclear atypia was obvious (bar =50 μ m).

have affected the patient's breathing and lead to death due to dyspnea (8).

Despite the combination of potentially effective targeted drug therapies after the second surgical resection of the intraspinal metastases, the patient was not able to tolerate the side effects of multiple drugs, resulting in poor evaluation of the efficacy of these drugs. For this patient's metastatic tumor of entire CNS, we considered there may be two main reasons. (I) H3F3A mutation. H3F3A mutation is generally considered to be a character of DMG, which is mainly grows in the midline, and an important factor with poor prognosis (9,10). Patients diagnosed as DMG with H3F3A mutation was reported OS was approximately 9.4 months (11). Even with individualized targeted drug

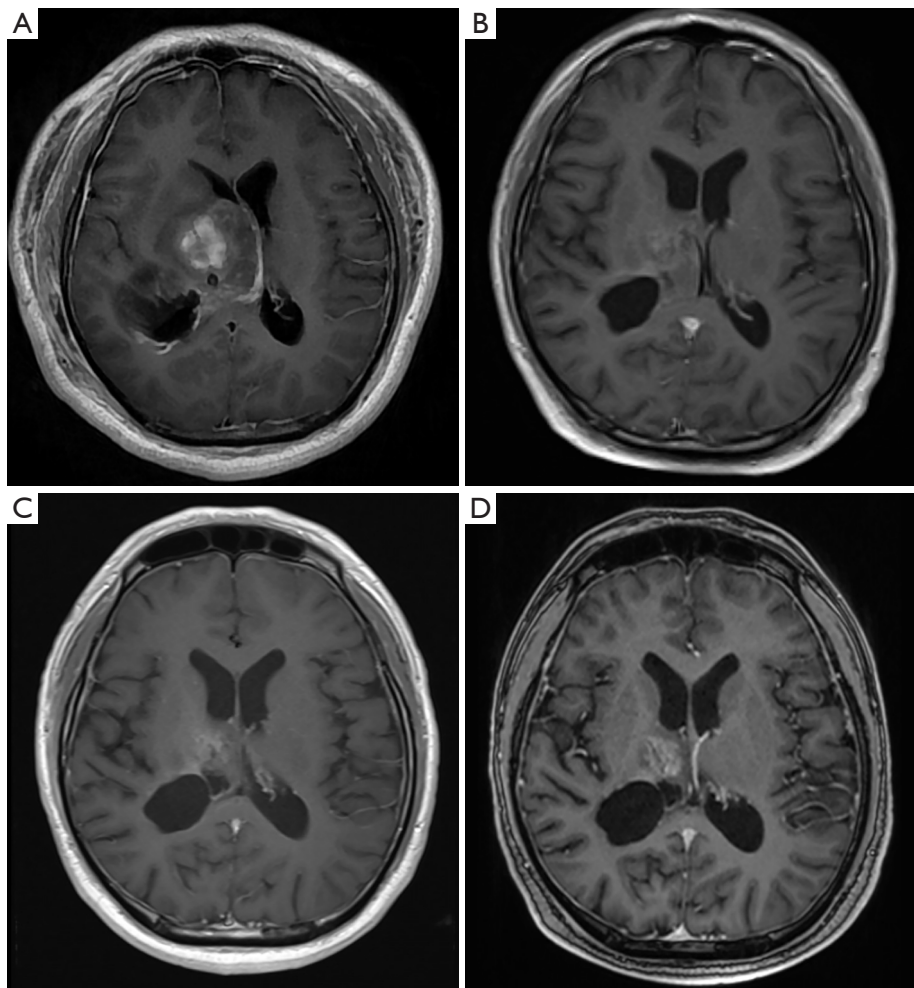


Figure 3 Postoperative MRI. (A) 72 h; (B) 2 months; (C) 5 months; (D) 8 months after surgery showing that the tumor was stable on enhanced MRI T1 sequence. MRI, magnetic resonance imaging.



Figure 4 Pre- and post-operative MRI in second surgery. (A) MRI T2 sequence showing a metastatic tumor (red arrow) on the L5 spinal cord pressing on the surrounding nerves 9 months after the initial operation; (B) postoperative T2 sequences showing that the tumor was completely removed. MRI, magnetic resonance imaging.

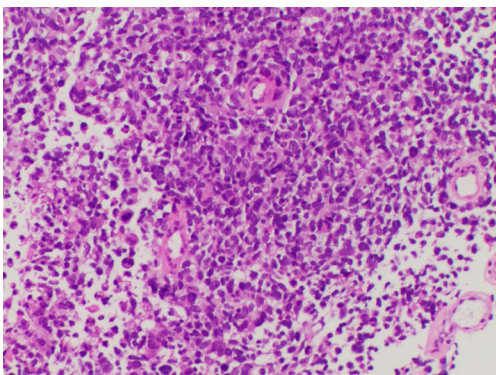


Figure 5 Light micrographs of the glioma. Tissue stained with H&E showing microvascular proliferation and necrosis (bar =200 μ m).

therapy, the prognosis is still poor. Gojo reported 12 cases of DMG patients who received personalized treatment, including inhibition of the PI3K/AKT/mTOR pathway, mitogen-activated protein kinase (MAPK) signaling, immunotherapy, receptor tyrosine kinase inhibition, and retinoic receptor agonist. The median time to progression in these patients was 29 weeks, and the median OS was 16.5 months (12). (II) Ventricle opening. In theory, the tumor cells will circulate along the CSF, carrying the tumor to other CNS sites, however, there is few case reported glioma with CNS metastasis before TTFields application. Of course, we can't rule out that the OS is prolonged after TTFields application, so we can observe more complication

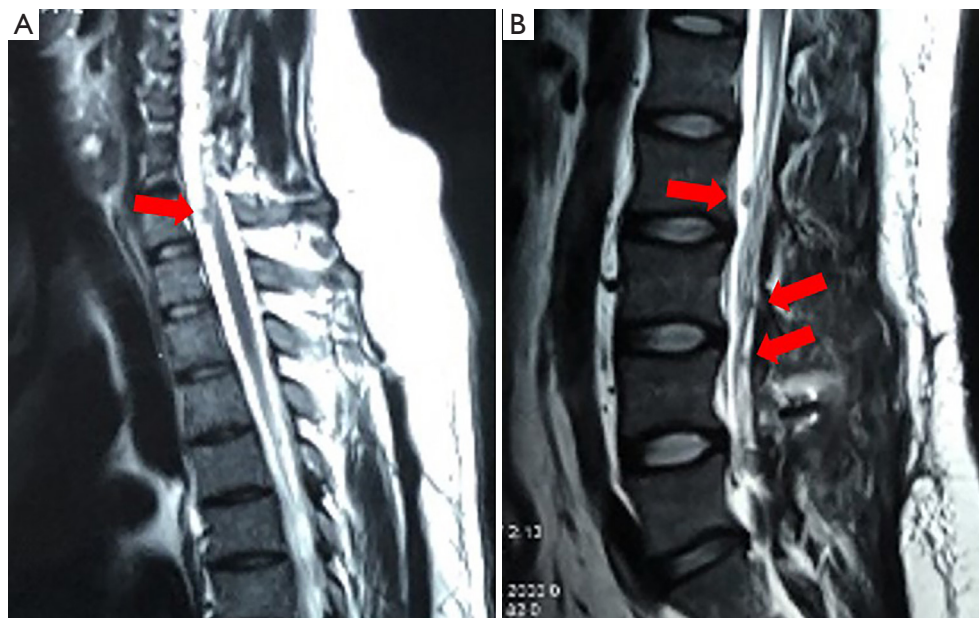


Figure 6 MRI T2 sequences showing four new metastases (red arrow) in the cervical 6 and lumbar 2–4 spinal cord. MRI, magnetic resonance imaging.

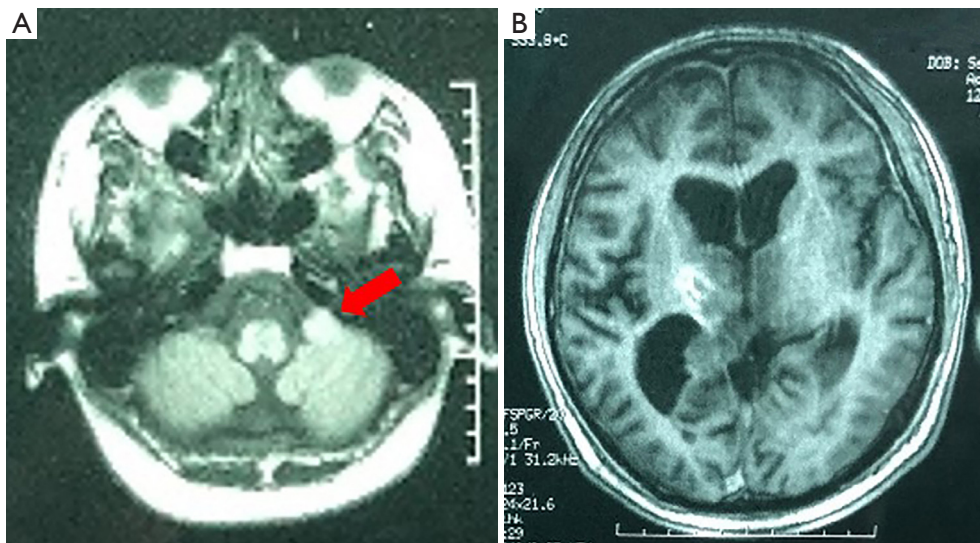


Figure 7 MRI T1 with contrast showing a new metastasis (red arrow) in the cerebellopontine angle and the enlarged original tumor in the right thalamus. MRI, magnetic resonance imaging.

that were not observed before.

With regards to the patient's entire treatment process, TTFields was very effective for primary thalamic tumor (13). This may be attributable to the fact that the thalamic tumor was stable when the patient was treated with TTFields continuously in the early stage, and recurred when the

TTFields was used irregularly or even discontinued in the later stage. In the EF-14 study, the Asian subgroup also showed efficacy and safety consistent with the general population. Kim reported that newly diagnosed GBM (ndGBM) patients in Korea participating in the EF-14 trial were similar to the entire EF-14 population (14).

However, TTFields could not cover the lesions under the tentorium, which is the focal challenge at present. TTFields has been approved by the FDA for the treatment of relapsed or ndGBM in the key clinical studies EF-11 and EF-14, both of which are supratentorial tumors (15). Therefore, the indications are only for supratentorial GBM. There are no large clinical trials of TTFields in supratentorial tumors, and only exploratory studies are available for reference. Professor Edwin investigated a series of alternative array configurations for the posterior fossa to determine the electric field coverage of a cerebellar GBM. The posteroanterior (PA) horizontal arrangement provided an average 46.6% increase in gross tumor volume (GTV) compared to supratentorial array when the PA array was placed initiating along the patient's posterior neck and horizontally parallel, along the longer axis, to the coronal plane of the patient's head (16). Further clinical studies of TTFields for subtentorial tumors are expected in the future.

In this case, the tumor in the primary thalamic site was stabled when the utilization rate of TTFields was high in the early stage, while the tumor recurred significantly when the utilization rate decreased or even stopped. Professor Toms has suggested that efficacy of TTFields was positively correlated with duration of use (17). In the study, TTFields were most effective when used for more than 18 hours per day. The median OS of patients with was 25 months (≥ 22 hours per day), and the 5-year OS increased from 4.5% to 29.3%. Therefore, some scholars propose to start using TTFields with CCRT as soon as possible. Currently, a small sample study shows that TTFields is safe to be used simultaneously in the stage of CCRT (18,19). A large phase III RCT study of ndGBM in the stage of CCRT combined with TTFields is compared with that without TTFields (EF-32, NCT: 04471844) is also in progress. The application timing of TTFields awaits further data generation in the future.

In addition, this case shows that patients with a skin disorder may tolerate TTFields treatment well, with a good quality of life (QOL) and no severe skin reactions to the therapy. However, metastasis in other areas result in corresponding nerve root symptoms, leading to the deterioration of the QOL of patients (20). In the EF-14 study of ndGBM, TTFields in combination with TMZ was found to significantly improve survival versus TMZ alone (17). To achieve an optimal response, TTFields therapy should be used on a continuous basis for a minimum of 18 hours a day. Although patients almost experienced TTFields-related skin adverse reactions. In

a retrospective safety review of TTFields after marketing (10/2011–2/2019) (21), 63% of 11029 patients with brain tumors treated with TTFields reported ≥ 1 AE. Stratified by diagnosis, 65% of ndGBM, 60% of recurrent GBM (rGBM), 65% of anaplastic astrocytoma and anaplastic oligodendroglioma, and 61% of other reported brain tumors reported ≥ 1 AE. When stratified by age, 58% of children, 63% of adults, and 66% of elderly patients reported ≥ 1 AE. Overall, AEs with an incidence of $\geq 5\%$ reported in all cohorts was comparable in diagnosis and age subgroups. Skin disorders (36%), general/application site disorders (31%), and neurological disorders (27%) were the most frequently reported adverse reactions among all patients, with similar rates in diagnosis and age subgroups. There no other TTFields-related toxicities were observed without an increase in radiation therapy or TMZ related toxicities as a result of combining TTFields with these therapies.

TTFields is a promising therapeutic approach for GBM patients, but there are still difficulties for subtentorial tumor, which requires further exploration and research. However, the significance of individualized targeted therapy is not clear, and the number of cases needs to be further expanded to obtain a more precise conclusion.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/atm-21-4395>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in

accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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