

Spinal cord metastasis in a long-term survivor of primary malignant glioblastoma: A case report

PENGWEI HOU^{1*}, MEIYAN LIU^{2*}, ZIQI LI³, MINGFA CAI¹ and CHENZHU CAI¹

¹Department of Neurosurgery, Shanghai Sixth People's Hospital Fujian, Jinjiang, Fujian 362200, P.R. China;

²Department of Hepatology, Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, Fujian 350025, P.R. China;

³Department of Neurosurgery, Fuzong Clinical Medical College of Fujian Medical University, Fuzhou, Fujian 350025, P.R. China

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Abstract. Glioblastoma (GBM) is the most common type of primary malignant brain tumor. Extracranial metastasis (ECM) is rare and usually indicates poor prognosis. We report a case of a 31-year-old female with GBM who underwent gross total resection followed by standard chemoradiotherapy. For recurrence, she received tumor treating fields and bevacizumab. At 23 months post-surgery, she developed COVID-19 pneumonia treated with dexamethasone, followed by spinal symptoms. MRI revealed L1-L2 lesions, and pathology after lumbar surgery confirmed ECM. Despite further treatment, the patient died of respiratory failure at 28 months. The present case illustrates the aggressive nature of ECM in GBM and the limited efficacy of current therapies in metastatic settings. Surgical resection and chemoradiotherapy remain the mainstay, while emerging treatments may provide hope for recurrent cases. Supportive care plays a critical role in advanced disease stages.

Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumor, with a poor prognosis and a median survival time of 12-16 months (1-3). The majority of patients with this cancer experience local progression during the disease course. Extracranial metastasis (ECM) is a rare occurrence in GBM, with an estimated incidence of 0.4-2.0%. Common metastatic

sites include the lungs, lymph nodes, liver and spine (4,5). Despite its rarity, ECM has been reported in several case studies; however, its underlying mechanism is not fully understood (3-6). The prognosis for patients with ECM is poor due to limited treatment options. Current standard treatment methods include maximal safe surgical resection followed by adjuvant radiotherapy and chemotherapy, the latter of which typically consists of the oral alkylating agent temozolomide (Stupp regimen) (6,7). The present report documents a case of GBM with spinal metastasis after surgery in a patient who was treated with the standard therapeutic regiment, including tumor treating fields (TTF), achieving an overall survival time of 28 months. The present study describes a rare occurrence of extracranial metastasis, highlighting the need for further investigation into potential mechanisms and novel therapeutic strategies.

Case report

A 31-year-old female patient presented with a 1-month history of recurrent headaches and dizziness. In November 2020, the patient began experiencing headaches and dizziness, characterized by a sensation of fullness in the head accompanied by lightheadedness, gradually worsening over time. Therefore, in December 2020, the patient visited the Department of Neurosurgery, Fuzong Clinical Medical College of Fujian Medical University (Fuzhou, China). The patient had no history of immunosuppressive drug use, intravenous drug abuse, organ transplantation or high-risk sexual behavior. Additionally, there were no other sensory or motor deficits. Routine laboratory tests revealed that all parameters were within normal ranges, with serological tests for human immunodeficiency virus, hepatitis B virus and hepatitis C virus being negative. Brain MRI with contrast revealed a right frontal lobe mass measuring 3.8x3.4 cm (Fig. 1). In addition, high-signal intensity on T2-weighted imaging (T2WI), a slightly low signal on T1-weighted imaging (T1WI) and a slightly high signal on diffusion-weighted imaging, with a surrounding area of patchy edema, were observed. Chest CT and abdominal ultrasound did not yield abnormalities, and no other space-occupying lesions were found in other organs.

A craniotomy was subsequently performed and the lesion was completely resected. Formalin-fixed, paraffin-embedded

Correspondence to: Professor Chenzhu Cai or Mr. Mingfa Cai, Department of Neurosurgery, Shanghai Sixth People's Hospital Fujian, 16 Jinguang Road, Luochang Street, Jinjiang, Fujian 362200, P.R. China

E-mail: chenzhu1234578@163.com

E-mail: caimingfa0412@163.com

*Contributed equally

Abbreviations: ECM, extracranial metastasis; GBM, glioblastoma; TTF, tumor treating fields

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tissue sections (4 μ m thick) were stained with hematoxylin and eosin (H&E) using standard protocols. Briefly, tissues were fixed in 10% neutral buffered formalin at room temperature for 24 h, followed by routine processing. Sections were stained with hematoxylin at room temperature for 5 min, rinsed, and counterstained with eosin for 1 min. Slides were examined under a bright-field microscope) revealed extensive necrosis with scattered pleomorphic cells, consistent with GBM, specifically giant cell GBM. Molecular pathological report results of the right frontal lobe (Table I) showed isocitrate dehydrogenase 1 (IDH1) wild-type and O6-methylguanine-DNA methyltransferase (MGMT)-positive methylation, confirming the diagnosis of GBM (World Health Organization grade IV) (8). The final diagnosis was therefore GBM (*IDH* wild-type and *MGMT* methylation-positive).

The postoperative chemoradiotherapy regimen was as follows: i) Radiation therapy, 2 Gy/session 5 days per week for 6 weeks, with a total dose of 60 Gy; and ii) temozolomide, 75 mg/m² per day 7 days per week, followed by maintenance temozolomide at 150 mg/m² for 5 days every 28 days for a total of 6 cycles. During the chemoradiotherapy, the patient experienced grade III chemotherapy-induced myelosuppression, which improved after symptomatic treatment, such as white blood cell stimulating therapy. In total, ~4 months after diagnosis, the treating physician decided to add TTF to the standard Stupp regimen, given the patient's tolerance to the treatment. In addition, ~15 months after diagnosis, after a multidisciplinary team consultation, bevacizumab 10 mg/kg was added to the treatment plan, administered every 21 days for 13 cycles. Follow-up brain MRI scans every 2-3 months showed no recurrence of the tumor.

At 23 months post-surgery, the patient contracted coronavirus disease 2019 (COVID-19) and developed severe bilateral pneumonia. After receiving a 10-day course of corticosteroid therapy (5 mg dexamethasone) for COVID-19 at the First Affiliated Hospital of Fujian Medical University, the patient recovered and was transferred to the 900th Hospital of the PLA for further treatment of GBM (Fig. 2). At 25 months post-surgery, the patient developed facial swelling and bilateral lower limb edema with pain. Although the patient had received dexamethasone treatment, the potential adverse impact of corticosteroids on GBM progression could not be excluded, and recurrence or metastasis was suspected. Therefore, an MRI scan of the lumbar spine (Fig. 3C) was performed, revealing an abnormal oval-shaped signal at the L1-L2 vertebral level with dimensions of 1.6x2.4x4.3 cm. The lesion showed isointensity on T1WI, a slightly high signal on T2WI and a number of low signals at the edges. No metastasis was observed in other locations. The suspicion was that the patient was suffering from a malignant GBM with ECM, as the patient exhibited symptoms indicative of spinal metastasis, such as persistent lower back pain, recurrent flatulence and ultimately, quadriplegia. Despite the severity of the condition, the patient opted to continue treatment. At 26 months after the initial diagnosis of GBM, the patient underwent further surgery for resection of the L1-L2 vertebral canal tumor. The strong vimentin expression, high Ki-67 proliferation index, ATRX loss, p53 mutation, and retained H3K27Me3 are all consistent with glioblastoma. These features, alongside the overall pattern of marker expression, strongly suggest that the

lumbar spinal metastasis is derived from a primary glioblastoma (Table II), confirming the diagnosis of ECM (Fig. 3D).

Postoperatively, the patient continued to experience severe pain, with a Numerical Rating Scale (9,10) score of 9. Despite receiving an intrathecal pain pump from the Department of Anesthesiology, the pain persisted, with a Critical Care Pain Observation Tool (11) score of 8-9. The patient abandoned the treatment and opted for conservative management limited to the maintenance of vital signs, before succumbing to respiratory and cardiac arrest from multiple site (brainstem) metastasis (Fig. 4). The survival time from diagnosis to mortality was 28 months, with a survival time of 2 months from ECM to mortality.

Discussion

GBM is the most common type of malignant brain tumor, accounting for ~49% of primary malignant brain tumors in the United States (1). The 5-year overall survival rate is 6.8% (2) and the prognosis is poor, with a median survival time of 12-16 months (3). One of the main characteristics of GBM is its diffuse and highly invasive nature, with postoperative recurrence being common. However, ECM is rare, with an estimated incidence of 0.4-2.0%, and the most commonly affected sites being the lungs, lymph nodes, liver and spine (4,5). The rarity of ECM may be attributed to the presence of the blood-brain barrier (BBB) and dura mater, and the lack of a lymphatic system. The low incidence rate of ECM may also be due to the short survival time of patients with GBM, who will typically succumb to complications before ECM can occur (12-15).

Although ECM is rare, cases of it continue to emerge, with the proposed mechanisms including hematogenous spread or direct seeding (16). Since the first report in 1928 of glioma recurrence with pulmonary metastasis (17), various types of glioma ECM have been reported, with GBM being more common in comparison to other primary intracranial tumors with ECM (18).

The mechanisms of ECM in GBM remain poorly understood, but risk factors have been widely described, including previous craniotomy or biopsy, ventriculoperitoneal shunt, younger age, radiation therapy, prolonged survival time, genetic mutations, tumor recurrence and the presence of gliosarcomatous components (17). In total, 90% of reported cases of ECM in GBM have undergone craniotomy. Hamilton *et al* (19) previously suggested that craniotomy can cause iatrogenic extracranial structural pathways, including ventriculoperitoneal shunt procedures, which can disrupt normal anatomical barriers, leading to tumor cell dissemination through the bloodstream (20). Although the majority of ECM cases are associated with surgery, there have also been reports of patients who developed ECM prior to surgery (21). This occurrence is hypothesized to be associated with various mechanisms, such as glioma angiogenesis inhibition and escape during tumor chemoradiotherapy (22), where primary tumor growth is suppressed but tumor cell invasion and proliferation increase near the brain tissue. Piccirilli *et al* (23) previously reported 128 cases of GBM with ECM, with a mean patient age of 40 years at the time of diagnosis, patients without ECM had a mean age of 54 years at diagnosis (24). Younger patients are therefore hypothesized to be more likely

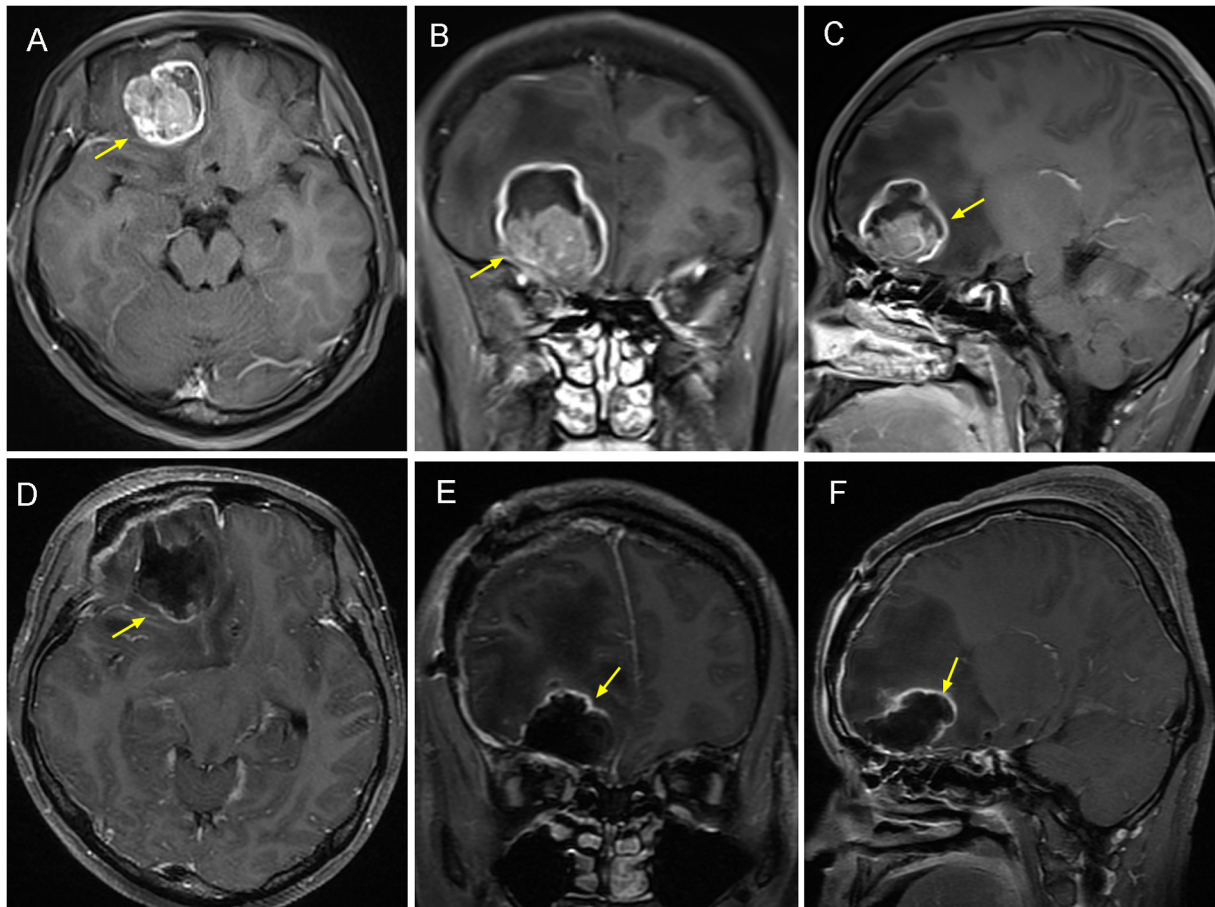


Figure 1. Preoperative and postoperative imaging of the intracranial tumor. (A) Axial contrast-enhanced MRI showing a right frontal lobe lesion with surrounding edema. (B) Coronal contrast-enhanced MRI showing the extent of the lesion. (C) Sagittal contrast-enhanced MRI revealing the mass effect and surrounding edema. (D) Axial contrast-enhanced MRI at 2 weeks post-surgery showing no residual tumor. (E) Coronal contrast-enhanced MRI confirming complete resection of the right frontal lesion. (F) Sagittal contrast-enhanced MRI indicating postoperative changes without evidence of tumor. The yellow arrows indicate the location of the tumor.

to develop ECM compared with older patients with chronic diseases, as they provide more time for tumor cells to escape the brain and form distant metastases (25,26). With advancements in treatment and diagnostic technology, the survival time of patients with GBM has increased, which also widens the time window for potential metastasis. Prolonged survival increases the possibility of GBM cells shedding into the lymphatic and circulatory systems (27,28). Andersen *et al* (29) reported that 7.8% of patients with primary gliomas that metastasized to the meninges had sarcomatous components. It is suggested that GBM with sarcomatous or mesenchymal features may promote ECM (30). Additionally, genomic studies (30-32) have reported associations with longer survival in patients with GBM and mutations in *TP53*, *RBI*, *ATRX*, *PTEN*, *TERT* and *IDH1*. The patient in the present case was relatively young, underwent craniotomy and radiotherapy at initial diagnosis, and had a longer survival time than average (12-16 months), consequently presenting risk factors for ECM. Furthermore, the surgical specimen from the spinal canal resection clearly demonstrated GBM dissemination.

ECM of GBM is relatively rare, with spinal cord metastases demonstrating an incidence rate of 20-40% in post-mortem examinations. This elevated incidence associates with the short survival periods of patients (33-35). The most frequent

anatomical sites for spinal metastases involve the lower thoracic, upper lumbar and lumbosacral junction regions (36). The current case presented with metastases at the L1-L2 spinal canal, consistent with these documented locations.

The clinical manifestations of GBM are determined by tumor location and proliferation rate. Spinal metastases typically present with sensory symptoms, radicular pain, back pain, paraparesis, quadriplegia, paraplegia and bowel/bladder dysfunction with sexual impairment (37). The most frequently reported symptom remains paraparesis, as previously documented by Schwaninger *et al* (38), where it was predominantly observed in younger patients. The present case developed these characteristic spinal metastatic symptoms progressively in latter disease stages, including persistent lumbar pain, recurrent intestinal distension and eventual progression to complete quadriplegia.

Patients with spinal metastases from GBM demonstrate a median survival of ~1 year, typically succumbing within months of symptom onset, reflecting the poor prognosis associated with this condition. Regarding the treatment of GBM, it does not differ based on histological subtype. The patient in the present case was diagnosed with giant cell GBM (*IDH* wild-type and *MGMT* methylated), where the treatment approach was consistent with that of other histological

Table I. Immunohistochemistry results of the right frontal lobe mass provided by the Department of Pathology.

Antibody type	Staining location	Staining intensity	Description
H3K27Me3	Nucleus	+++	
Ki-67	Nucleus	60%	
Vimentin	Cytoplasm	++++	
Glial fibrillary acidic protein	Cytoplasm	+++	
Oligodendrocyte transcription factor 2	Nucleus	++	
p53	Nucleus	90%	
CD34	Membrane	Small foci+	
ATRX	Nucleus	+	Mutation
PTEN	Cytoplasm	+++	
S-100	Cytoplasm/nucleus	++	
Synaptophysin	Cytoplasm	+	

Sanger sequencing revealed that both *IDH1* and *IDH2* genes were wild-type, fluorescence PCR revealed that O6-methylguanine-DNA methyltransferase methylation was positive, and fluorescence *in situ* hybridization demonstrated there was no co-deletion of 1p/19q. Amplification refractory mutation system fluorescence analysis showed no *BRAF V600E* mutation, and fluorescence *in situ* hybridization analysis demonstrated no epidermal growth factor receptor gene amplification. *IDH*, isocitrate dehydrogenase.

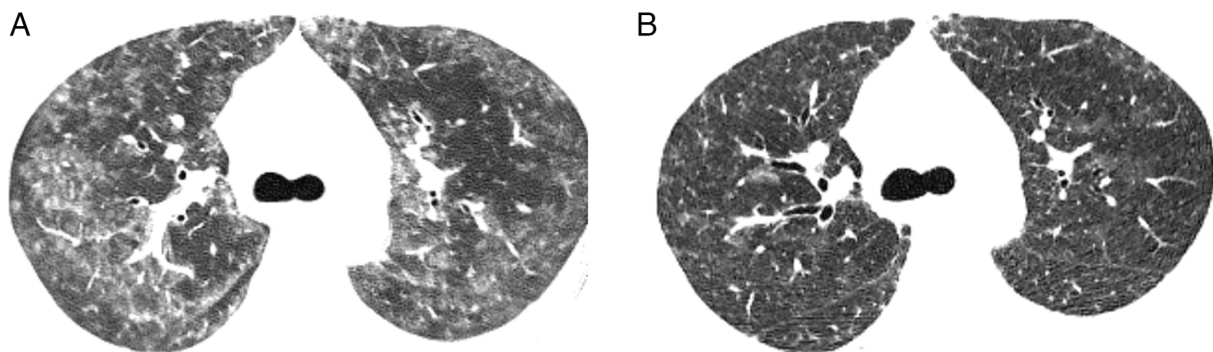


Figure 2. CT chest images of the lung. (A) Pneumonia following coronavirus disease 2019 infection. (B) Chest CT after high-dose steroid shock therapy. After referral to the 900th Hospital of PLA, the pulmonary inflammation had mostly resolved.

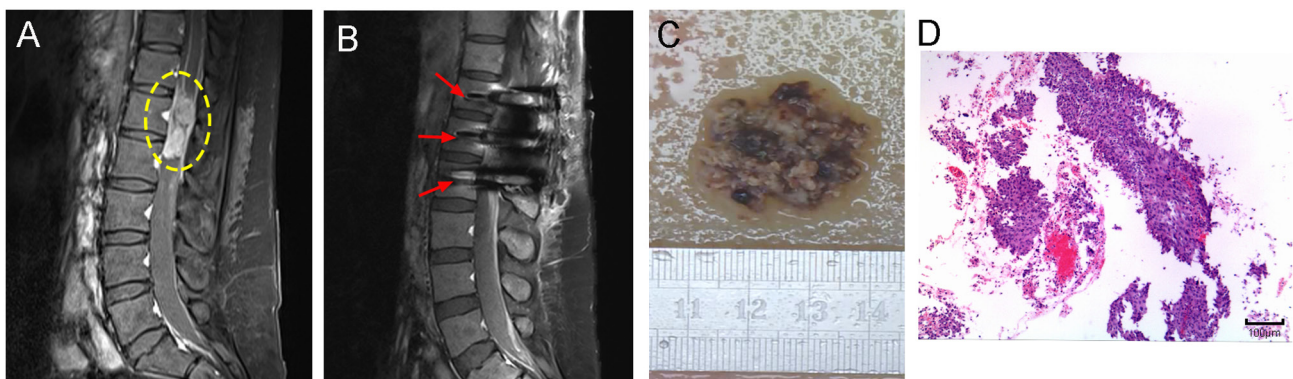


Figure 3. GBM spine metastasis. (A) Enhanced MRI showing tumor invasion at the L1-L2 vertebral level, with a high signal intensity on T2-weighted imaging and uneven enhancement on contrast scans. (B) Postoperative MRI of the lumbar spine showing an *in situ* thoracolumbar fixation at T12-L1, with a clear spinal canal and no marked compression of the subarachnoid space. (C) Surgically resected lumbar spinal tumor. (D) Hematoxylin and eosin staining showing necrosis and scattered pleomorphic cells, suggesting dissemination of a poorly differentiated GBM (magnification, x40). GBM, glioblastoma.

subtypes. The standard treatment for GBM at initial diagnosis includes surgery, temozolomide-based concurrent radiotherapy and further adjuvant temozolomide therapy (6). Surgical

resection allows for accurate histopathological diagnosis, tumor gene profiling and a reduction in tumor volume, which is beneficial for postoperative radiotherapy. In addition, TTF

Table II. Molecular pathological report results of lumbar spinal tumor.

Antibody type	Staining location	Antibody staining intensity	Description
Vimentin	Cytoplasm	++++	Focally scattered positive
Glial fibrillary acidic protein	Cytoplasm	+	
Somatostatin receptor-2	Cytoplasm	+	
ATRX	Cytoplasm	+	
Ki-67	Nucleus	80%	Mutant type
Integrase interactor 1	Nucleus	++++	
S-100	Nucleus	Few +	
p53	Cytoplasm/nucleus	80%	
Epithelial membrane antigen	Nucleus	Few +	
H3K27Me3	Cytoplasm	++++	

O6-methylguanine-DNA methyltransferase methylation was positive. Sanger sequencing of the telomerase reverse transcriptase gene promoter region showed that it was wild-type. Fluorescence *in situ* hybridization analysis did not detect epidermal growth factor receptor gene amplification or cyclin-dependent kinase inhibitor 2A deletion.

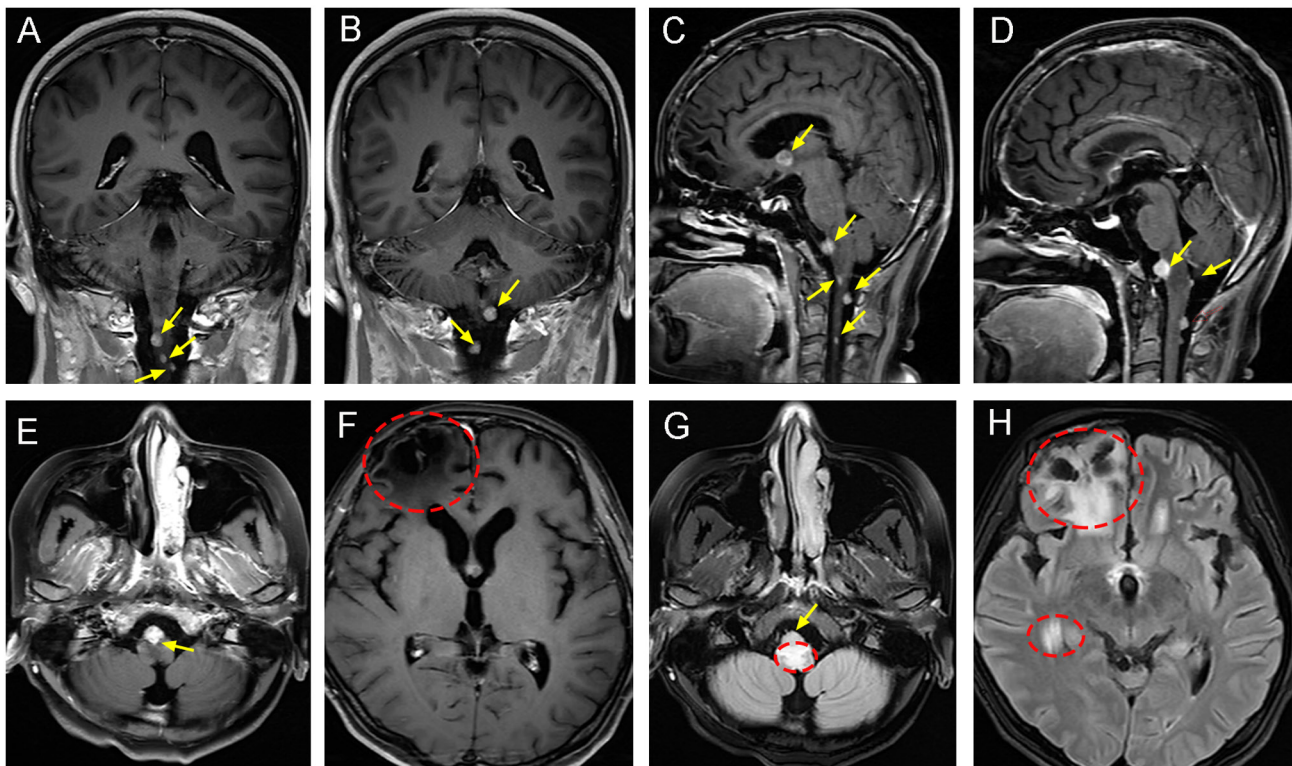


Figure 4. Tumor recurrence 8 months after lumbar spine surgery. (A) Coronal T1-weighted MRI showing recurrent lesion in the right frontal lobe. (B) Coronal T1-weighted MRI demonstrating surrounding edema. (C) Sagittal T1-weighted MRI displaying tumor recurrence along the surgical margin. (D) Sagittal T1-weighted MRI showing adjacent tissue compression. (E) Axial T1-weighted MRI revealing enhanced recurrent lesion. (F) Axial T1-weighted MRI indicating associated mass effect. (G) Axial diffusion-weighted imaging (DWI) showing restricted diffusion in the lesion. (H) Axial DWI confirming high signal intensity consistent with tumor recurrence. The yellow arrows indicate the tumor lesion and the red circles indicate the edema around the tumor.

provide low-intensity alternating electric fields, which have been approved for use in combination with temozolomide as an adjuvant treatment. TTF is primarily used as an anti-mitotic therapy, with its use during temozolomide maintenance being shown to extend survival time in patients with supratentorial disease (7). However, the high cost, treatment adherence issues and skin toxicity are barriers to the clinical application of TTF. The United States Food and Drug Administration

has approved the use of TTF as an option for eligible patients who are willing to undergo this treatment. The patient in the present case started TTF therapy ~4 months after diagnosis, which may be one reason for the extended survival time.

After standard concurrent chemoradiotherapy and adjuvant chemotherapy, the majority of patients with GBM will typically experience recurrence within 6 months (6). For recurrent or metastatic disease, further surgical resection, re-irradiation,

systemic treatments (lomustine or bevacizumab), combination therapy or supportive care, particularly for younger patients with good performance status, can be considered (39,40). The treatment plan in the present case, both at initial diagnosis and after recurrence, followed the current treatment guidelines (41). Regarding the use of bevacizumab for anti-angiogenesis in patients with GBM, Lah *et al* (42) suggests that this treatment is associated with early ECM in patients with GBM (42), where long-term use may increase tumor aggressiveness (43). To this effect, two large randomized trials in 2014 confirmed that although bevacizumab prolonged progression-free survival, it did not improve overall survival and it increased the incidence of adverse events (hypertension and thromboembolism) (44,45). The present patient underwent 13 cycles of bevacizumab treatment, but the condition worsened with lumbar metastasis, and the possibility of bevacizumab-induced hypoxia and tumor-associated macrophage involvement could not be excluded. Due to the lack of notable therapeutic benefits from bevacizumab (46), the European Medicines Agency has rejected its use in patients with recurrent GBM, and the present patient did not receive further bevacizumab treatment.

Furthermore, the use of corticosteroids, such as dexamethasone, may decrease the therapeutic efficacy of chemotherapy and radiotherapy in GBM patients and potentially shorten survival, thereby negatively impacting prognosis. This may be due to the protective effect of dexamethasone against the anti-proliferative action of radiotherapy and chemotherapy (which causes genetic toxicity stress) (47). Corticosteroids can cause morbidity, including steroid myopathy, immune dysfunction, adrenal insufficiency and bowel perforation, and mortality through their direct toxicity. Previous meta-analyses have shown that corticosteroids can inhibit antitumor immune responses in glioma and increase the risk of mortality in patients with GBM (48-51). High blood glucose (52) and muscle wasting (53) are risk factors for poor survival outcomes, treatment discontinuation and decreased progression-free survival time. The present patient received dexamethasone treatment for COVID-19 pneumonia 23 months after the initial surgery. However, no tumor recurrence was observed during outpatient follow-ups. After 2 months of corticosteroid use, the patient presented with bilateral lower limb edema and lumbar pain, and was found to have distant lumbar metastasis. The possibility that corticosteroids accelerated the tumor progression and shortened the patient's survival time cannot be excluded.

ECM of GBM progresses rapidly, has a poor prognosis and lacks a definitive treatment protocol. Despite using all available treatment options, the present patient succumbed, with only a 2-month survival time between the ECM diagnosis and mortality. Compared with solid tumors, metastatic GBM presents with notable treatment challenges in terms of biological factors, such as the BBB, and the unique tumor and immune microenvironment (54). Current research has focused on immunotherapy and precision oncology, such as immune checkpoint therapy (CD73) (55), chimeric antigen receptor T-cell therapy (56) and TAT-Cx43266-283 (an Src-inhibiting peptide with antitumor properties in preclinical GBM models) (57). Nanomedicine offers innovative diagnostic strategies for GBM, including the use of nanoparticle-based contrast agents to enhance MRI resolution, and nanosensors for detecting circulating tumor biomarkers with high specificity

and sensitivity. Magnetic nanoparticles or their composites have proven effective in simultaneously inducing ferroptosis and enabling MRI imaging, demonstrating remarkable potential in the suppression of glioblastoma (GBM) (58,59).

In conclusion, although ECM in GBM is rare, its prognosis is poor and the associated survival time is short; therefore, surgeons should be vigilant regarding the possibility of ECM. At present, surgical resection and concurrent chemoradiotherapy remain the first-line treatments for GBM. Therefore, achieving a gross total resection during surgery to reduce the possibility of ECM should be prioritized. Several novel therapies have shown promising results in cases of recurrence or metastasis, but there remains a need for enhanced supportive care and treatment to improve the patient's quality of life and survival outcomes.

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Availability of data and materials

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

Authors' contributions

PH, ML and ZL analyzed the data, and reviewed and edited the manuscript. ML obtained medical images. ZL and MC advised on patient treatment or analyzed patient data. MC and CC contributed to the study methodology, supervision, validation, reviewing and editing. PH, ML, ZL, MC and CC confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The husband of the patient provided written informed consent for publication of the medical data and images.

Competing interests

The authors declare that they have no competing interests.

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