Case Report

A personalized integrative approach to recurrent glioblastoma: Exploring the role of cannabinoids and hyperbaric oxygen in a real-world case

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ABSTRACT

Glioblastoma multiforme (GBM) is the most aggressive form of primary brain tumor in adults, associated with poor prognosis and high recurrence rates despite multimodal standard therapies. Cannabinoid therapy has recently emerged as a potential adjuvant due to its anti-tumor properties. We present a 68-year-old male with recurrent right temporal lobe GBM (World Health Organization Grade 4), previously managed with craniotomy and radiotherapy. Following recurrence, a personalized integrative approach using temozolomide, oral cannabinoids (tetrahydrocannabinol/cannabidiol), and hyperbaric oxygen therapy (HBOT) was initiated at our center. The patient showed a 38.25% reduction in tumor volume, significant clinical improvement, and resolution of symptoms without adverse effects. The integrative use of temozolomide, cannabinoids, and HBOT appears promising in recurrent GBM management. The case highlights the need for further exploration of cannabinoid-based and adjunctive therapies in glioblastoma treatment.

Key words: Cannabinoids, Glioblastoma, Hyperbaric oxygen Therapy, Temozolomide

Glioblastoma multiforme (GBM), the World Health Organization (WHO) Grade 4 astrocytoma, is the most common and aggressive primary brain tumor in adults [1]. GBM remains one of the most aggressive and treatment-resistant primary brain tumors, with recurrence being almost inevitable, despite standard multimodal therapies involving surgery, radiotherapy, and temozolomide. Given the poor prognosis and limited therapeutic options at recurrence, there is an urgent need to explore novel, integrative, and patient-centered treatment strategies.

We present a case of recurrent GBM in a 68-year-old male managed with a novel combination therapy involving standard temozolomide, cannabinoids (tetrahydrocannabinol [THC]/cannabidiol [CBD]), and hyperbaric oxygen therapy (HBOT), showing significant clinical and radiological improvement. THC and CBD have antitumor effects, including apoptosis induction, cell proliferation, inhibition, and antiangiogenesis. This case is presented to document and highlight the potential benefits of combining conventional chemotherapy with two emerging adjunctive therapies–cannabinoids (THC/CBD) and HBOT–in a patient with recurrent GBM who was not amenable to repeat surgical intervention. This case adds to the limited but growing body of evidence supporting the incorporation of non-conventional therapies in glioblastoma management and demonstrates how such an approach may offer clinical, radiological, and symptomatic improvement in a challenging recurrence scenario.

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CASE PRESENTATION

A 68-year-old man presented with complaints of recurrent headaches, neck pain, irritability, mood swings, and weakness on the right side of his body to StemRx Bioscience Solutions Pvt. Ltd (Navi Mumbai, India) after undergoing surgery to treat his right temporal lobe glioblastoma, WHO grade 4. Before admission, a diagnosis of recurrent glioblastoma was made at our facility. On December 19, 2021, the patient had a right frontotemporoparietal craniotomy, and the tumor was removed.

Excision biopsy of the right middle temporal region was done, and the tumor cells exhibit the following immunostains: GFAP S 100: Positive, IDH1: Negative, and ATRX: Negative (most tumor cells retain nuclear stain, with scattered loss in certain regions). Ki-67: Proliferation index was focally up to 35%; P53: negative

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(5% nuclei positive). 67: Up to 35% of the proliferation index was focused; P53: Negative (5% of nuclei are positive). The usage of phenytoin, which was given to treat post-operative seizures, caused the patient to develop Stevens-Johnson syndrome (SJS) after surgery. After the medication was removed right away, the SJS skin lesions progressively disappeared. The patient and their family have explained the overall guarded prognosis in light of the STR and GBM histology report.

The team of onco-specialists and the patient's family agreed on hypofractionated extended beam radiation as a course of treatment because the patient was allergic to phenytoin and had recently recovered from the potentially fatal SJS. The patient experienced symptom relief for approximately 2–3 months, after which he repeatedly started experiencing headaches and weakness on one side of the body. Further investigations revealed recurrence, and the patient was informed of the limited therapeutic options and a poor prognosis.

A personalized treatment plan of chemotherapy, cannabinoids, and HBOT was planned for the patient under the guidance of an oncologist. Informed consent was obtained after explaining the planned combination therapy in detail. Consent was also obtained for the publication of this manuscript. Initially, dexamethasone (8 mg) and mannitol (100 cc) were prescribed to reduce brain edema and intracranial pressure. Temozolomide was chosen as the drug for chemotherapy, and the dose was calculated based on the body surface area of the patient (1.70 m^2). A dose of 75 mg/m^2/day, amounting to 133 mg/day, was administered. The patient was monitored around the clock to identify any adverse reactions, considering the history of SJS. In addition, the cannabinoids, THC and CBD, were prescribed in an oral form during chemotherapy. The dose was calculated based on a study conducted at Leeds University for patients with recurrent glioblastoma. Accordingly, twelve sprays were advised per day, each containing 2.7 mg THC and 2.5 mg CBD. The total daily dose of THC was 32 mg, and that of CBD was 30 mg for our patient. Furthermore, sessions of HBOT were administered.

The patient tolerated the treatments well and did not experience any side effects. He achieved significant relief from headache and neck pain within 2 days of the treatment. Physiotherapy was initiated simultaneously to manage the right-sided weakness and difficulty in performing daily living activities. With the regular rehabilitation protocol, the patient was able to perform fine motor movements more efficiently, his balance and gait improved, and he experienced an overall reduction in weakness within days. The combination of treatment and physiotherapy rehabilitation was continued. On day 20, a magnetic resonance imaging was taken that showed a definite decrease in the size of the lesion, as well as a reduction in edema and inflammation. The pre-treatment tumor size was 5.3 × 4.6 × 4.1 cm, volume was 58.42 cc, whereas the post-treatment tumor size was 4.2 × 4.1 × 4.0 cm, and volume was 36.07 cc, that's a 38.25% reduction in the volume of the tumor (Figs. 1-4).

On clinical examination, the patient had mild left hemiparesis and mild unsteadiness while walking. The patient was discharged on request from our center after 22 days after ensuring a stable general condition. The subsequent treatment plan was discussed with the oncologist, physician, and physiotherapist in the patient's

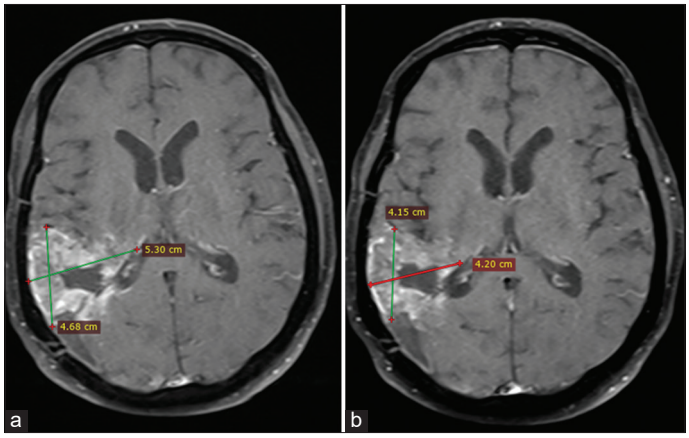

Figure 1: (a) Pre-treatment axial post-contrast T1-weighted image showing heterogeneously enhancing tumor volume 58.42 cc; (b) Post-treatment (day 20) axial post-contrast T1-weighted image showing reduction in the tumor size volume 36.07 cc

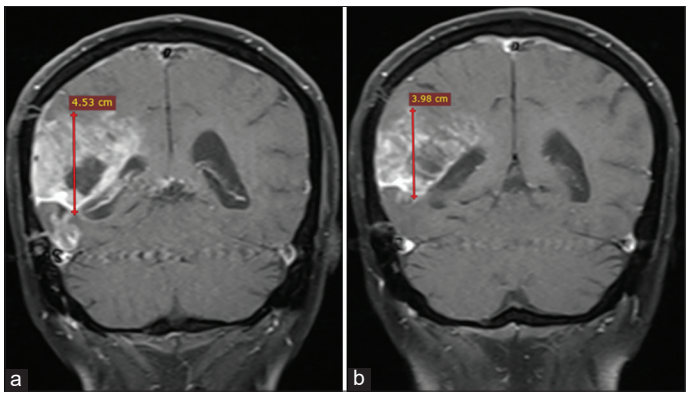

Figure 2: (a) Pre-treatment coronal post-contrast T1-weighted image showing heterogeneously enhancing tumor, volume 58.42 cc; (b) Post-treatment (day 20) coronal post-contrast T1-weighted image showing reduction in the tumor size volume 36.07 cc and degree of enhancement of the tumor

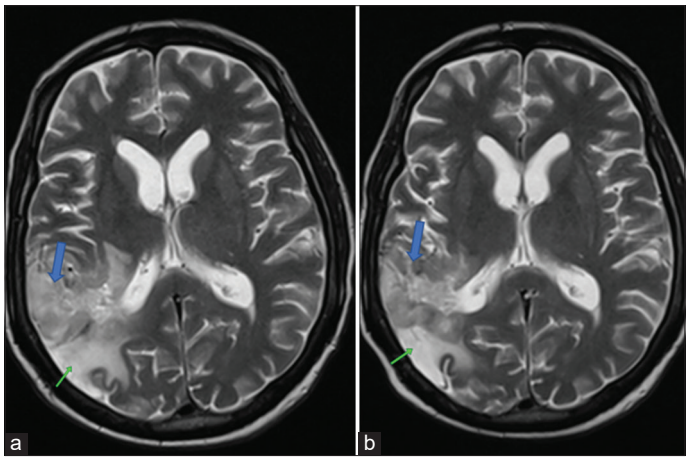

Figure 3: (a) Pre-treatment axial T2-weighted image showing the tumor (blue arrow) with surrounding edema (green arrow); (b) Post-treatment (day 20) axial T2-weighted image showing reduction in the tumor size (blue arrow) as well as the perilesional edema (green arrow)

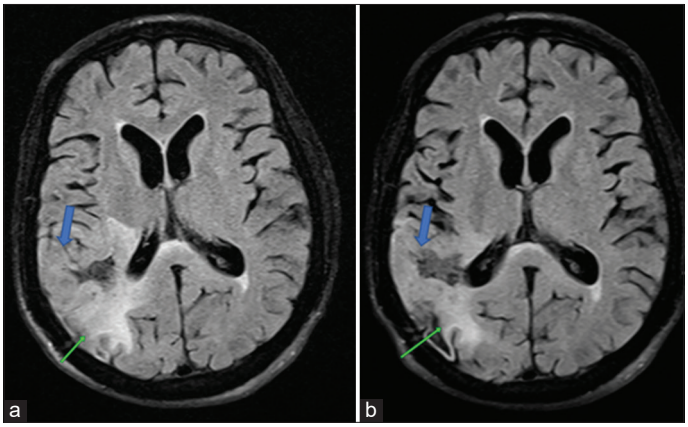

Figure 4: (a) Pre-treatment axial fluid-attenuated inversion recovery (FLAIR) image showing perilesional edema (green arrow); (b) Post-treatment (day 20) axial FLAIR image showing reduction in the perilesional edema (green arrow) and regression in the right ventricular compression

hometown. A consensus was reached that temozolomide should be continued for 5 days every month under the supervision of the oncologist. The patient was also instructed to continue THC 32 mg and CBD 30 mg orally once daily for 2 months, and the required quantity of the cannabinoids was given. The patient was instructed to continue the physiotherapy exercises at home (under the guidance of a physiotherapist, if required) to help maintain mobility and independence in performing daily living activities. The patient could not continue HBOT as he did not have a facility in his hometown. Telephone follow-up was conducted up to 60 days, and the patient was stable and asymptomatic. The patient continues maintenance therapy with cannabinoids and follow-up imaging.

DISCUSSION

In the past 30 years, the survival of patients with GBM has not improved and remains dismal, with a maximal survival known of up to 12–15 months due to its high recurrence and resistance to current combination therapies, including oncotomy, radiotherapy, and chemotherapy [2,3]. The 5-year survival rate is <5%. Light has been shed in recent years on the anticancer properties of cannabinoids from *Cannabis sativa* [2]. Surgical resection is often incomplete due to the proximity of the tumor to vital brain structures and infiltrative growth characteristics [3,4]. In GBM, surgery aims to not harm the patient rather than attempt to cure since the outcome is dismal. Treating the noncontiguous parts of the tumor remains a challenge after surgery.

Mammalian tissues contain an endogenous cannabinoid system, a homeostatic regulator of neurotransmitter activity, and at least two types of cannabinoid receptors, CB1 and CB2 [5]. THC mimics the endogenous substances, anandamide and 2-AG, by binding to the CB receptors, inducing different pathways, eventually leading to the reduction in tumor growth [6]. Inhibition of tumor cell migration and invasion occurs due to cannabinoids [7]. Cannabinoids reduce tumor progression via inhibition of tumor angiogenesis, tumor cell apoptotic death, and inhibition of cancer cell proliferation [8]. Cannabinoids can cause cell cycle arrest, inhibit cell proliferation, and elicit cell death, which leads to the prevention of tumor spread, inhibition of oxygen and nutrient supply, and a halt in angiogenesis of the tumor environment [9]. Activation of the CB1 receptor, by THC administration, induces sphingomyelin hydrolysis and sharp ceramide production within minutes, in glioma cells. CB2 receptor activation-induced apoptosis in glioma cells mostly relies on the prolonged build-up of ceramide, through enhanced de novo synthesis, which activates the Raf-1-MEK-ERK pathway leading to apoptosis [9]. As CBD acts independently of the CB receptors, it is believed that it increases the production of reactive oxygen species in cancer cells [10]. Cannabinoids have displayed a fair safety profile without any reported prolonged narcotic effects [2]. In our case, the tumor volume not only decreased by 38.25% but the perilesional edema was also decreased in a period as short as 20 days, which was very promising.

THC and CBD are known to cross the blood-brain barrier easily, giving them an edge in reaching the noncontiguous parts of the unresected tumor in patients treated surgically and also in patients who cannot undergo surgery. In such scenarios, THC and CBD can be used post-surgery, post-radiotherapy, and post-chemotherapy to prevent tumor recurrence. THC and CBD are oral drugs, safe, and cost-effective. Hypoxia, infiltrative growth, and angiogenesis are the biological hallmarks of GBM. Hyperbaric oxygen may be a modality to counter the hypoxic milieu of the tumor.

PubMed and Web of Science were used for online searches to find studies on combination therapy using temazolamide, hyperbaric oxygen, THC, and CBD simultaneously. There was no such combination used previously. Cannabinoids possess anticancer potencies against glioma cells. Aristocrat study is ongoing in using THC and CBD in GBM [11]. We feel there is an unmet need for better options in treating GBM, and further studies should explore its usage further, in combination with hyperbaric oxygen.

CONCLUSION

This case demonstrates that an integrative approach combining standard chemotherapy with cannabinoids and HBOT can be safe and potentially effective in managing recurrent GBM. The observed clinical and radiological improvements advocate for further investigation into such multimodal treatment strategies.

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