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**CASE STUDY: GLIOBLASTOMA MULTIFORME MANAGEMENT USING
INTEGRATED HEALTH CLINIC APPROACH**

Introduction:

Astrocytomas are highly infiltrative tumors that are graded by their degree of anaplasia. Low-grade tumors are classified as astrocytoma (WHO grade II), those with more evidence of cytologic atypia and increased cellularity as anaplastic astrocytoma (WHO grade III), and those with highly malignant features as glioblastoma (GBM; WHO grade IV)¹. Given the aggressive nature of high grade gliomas, they are often best managed with a combined modality approach, utilizing maximal resection, and adjuvant radiation therapy and chemotherapy, typically temozolomide (TMZ)². Due to the aggressive features of GBM, clinical outcomes are generally unsatisfactory, with 1 and 5 year survival averaging 35% and 5% respectively³. In this report, we present a case of GBM at Integrated Health Clinic (IHC), using loco-regional hyperthermia (LRHT) in conjunction with disease-specific dietary, supplementary, injection and intravenous therapies. Current literature has shown that hyperthermia can selectively target cancer cells through the application of several mechanisms of action^{4,5}. Malignant cells are more sensitive to high temperatures compared to healthy tissue⁶. The use of hyperthermia to treat cancer can be applied as an adjunctive therapy with various established cancer treatments such as radiotherapy and chemotherapy⁷.

Case history:

P.S., an otherwise healthy 46-year old male was diagnosed with GBM of the corpus callosum in 2010. He initially presented with progressive weakness of his right leg and eventually of the right hand, beginning in September 2010. A head CT was performed in December 2010 as symptoms continued to progress. Imaging revealed a midline mass in the area of the corpus callosum extending to the left side. An MRI of the head from January 2011 confirmed the presence of a 3.5 x 5.8 cm mass in the region of the corpus callosum. This was followed by a stereotactic-guided biopsy and pathology revealed glioblastoma with an oligodendroglial component. P.S. had an episode of deterioration of his right hemiparesis after the biopsy, which temporarily improved after oral dexamethasone of 2 mg BID. He continued to have weakness of his right extremities. There was also decline in short-term memory and personality changes.

P.S. completed 6 weeks of adjuvant chemo-radiotherapy with TMZ and 6,000cGY of radiation in 30 fractions, finishing in April 2012. He then received six cycles of TMZ

(300mg/day) daily, 5 days on and 23 days off (28 day cycle). A follow up scan on April 27, 2012 showed a partially calcified mass centered in the corpus callosum. Overall, it has not significantly changed in size or enhancement compared to January 2012 measuring 8 mm in AP dimension and 2.1 cm in width. Karnofsky Performance Status (KPS) after conventional therapy was 100. Alongside TMZ, P.S. in June 2012, began a low-glycemic modified ketogenic diet, high dose enzymes, boswellia serrata, dichloroacetate (DCA) 20mg/kg/day, loco-regional hyperthermia (LRHT) 3x/week for 4 weeks with intravenous ascorbic acid (IVAA) (25 gm) and dexamethasone 4mg QD beginning one week before LRHT and finishing one week after LRHT (Table 1.).

Table 1. Treatment Protocol

Medications	Dosage	Effect
Prescriptions		
Dichloroacetate (DCA)* (20mg/kg/day)	5 days on, 2 days off	Inhibiting pyruvate dehydrogenase kinase, increases the flux of pyruvate into the mitochondria, promoting glucose oxidation over glycolysis. This reverses the suppression of mitochondrial apoptosis in cancer and results in suppression of tumour growth ⁸ . Inhibits angiogenesis, alters expression of HIF, and alters pH regulators V-ATPase and MCT1 ⁹
Dexamethasone 4mg/day	Starting 1 week before and LRHT and finishing 1 week after LRHT	Inhibits glioma cell growth, neuroprotective effects in brain and reduces tumor-induced angiogenesis. Acts pleiotropically and impacts tumor growth, tumor vasculature and tumor-associated brain damage ¹⁰ . Decrease blood-brain barrier permeability and regional cerebral blood volume. Decrease edema in brain tumor ¹¹

Supplements		
Boswellia serrata*	2 capsules p.o. BID	Potentiates apoptosis, inhibits invasion, and abolishes osteoclastogenesis. Potent anti-inflammatory ¹² . Cytotoxic and apoptotic potential in cancer cells ¹³

Can-Arrest (boswellia, curcumin, quercetin)*	Boswellia 200mg Curcumin 200mg Quercetin 100mg 1 capsule p.o. BID	Inhibit cyclooxygenase-2 (COX2) enzymes. Blocking COX 2 has been shown to decrease tumor invasiveness ¹⁴ . Anticancer activity. Inhibition of the transcription factor NF-κB to arrest tumor growth and its progression ¹⁵ .
Wobenzyme	3-9 capsules TID (between meals)	Reduces inflammation and mitigates adverse effects of cytotoxic treatment ¹⁶ . Synergistic alongside radiation & prevents post-radiation fibrous changes ¹⁷
Melatonin	10mg capsule p.o. QHS	Multi-disciplinary anti-cancer action reduces toxicity after chemotherapy, radiotherapy, immunohormonal therapy and cancer surgery. Adjuvant therapy for cancer ¹⁸ . Immunomodulatory in the immunocompromised state ¹⁹

* Taken 1 hour prior to LRHT using daily dose

LRHT was administered from June 12, 2012 to July 7th 2012 with a total of 12 treatments completed. Treatments were well tolerated with no reported symptoms or side effects.

Based upon the scans, there was a improvement in his condition, which showed stable disease. A follow-up CT scan of the head with contrast complete on August 7, 2012 revealed a minimally enhancing partially calcified mass in the lateral ventricle measuring up to 2.1 x 2.2 x 1.5 cm in diameter compared to 8mm in AP dimension and 16mm in transverse dimension from April 2012 (Figure. 1, 2).

Figure 1. - CT scan of head August 7, 2012 - coronal plane

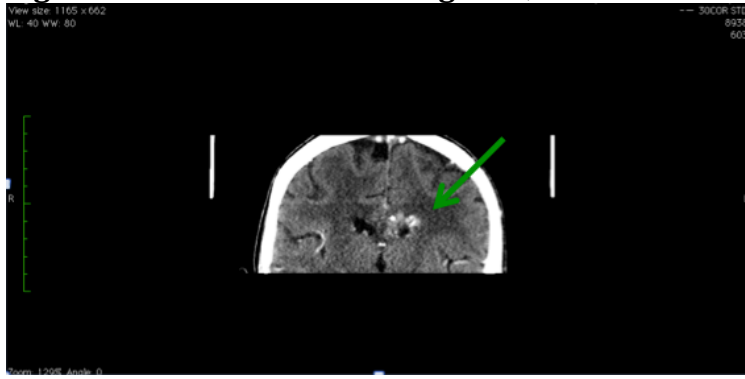
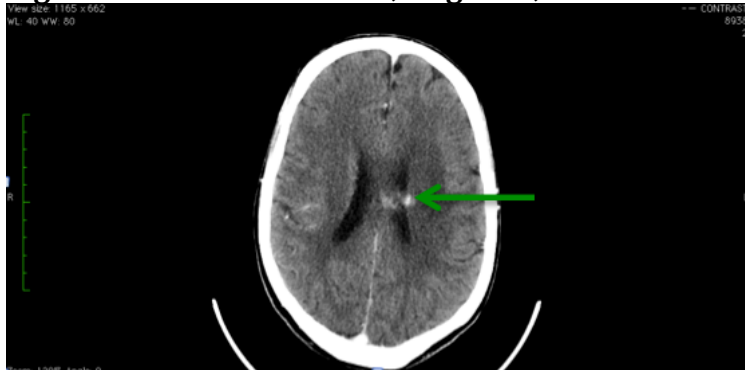


Figure 2. - CT scan of head, August 7, 2012 - transverse plane



A follow-up CT of the head from October 25, 2012 reported a stable appearance of the mass (Figure. 3, 4).

Figure 3. - CT scan of head October 25, 2012- coronal plane

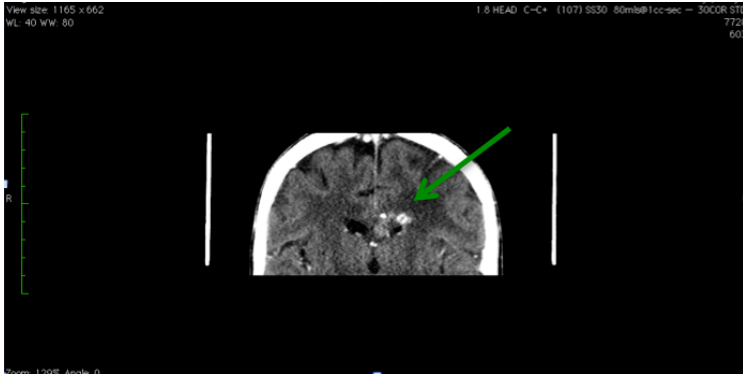
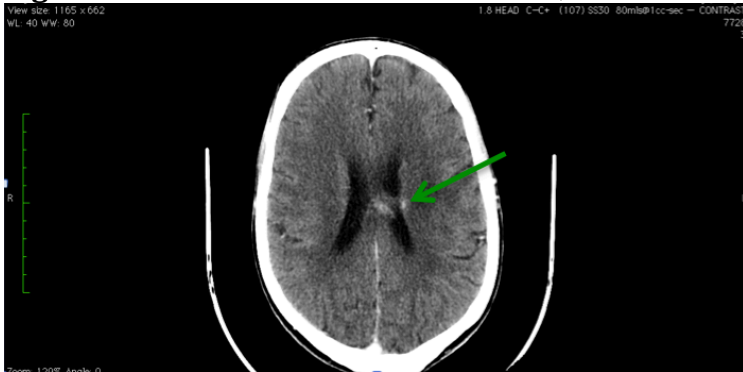


Figure 4. - CT scan of head October 25, 2012 - transverse plane



A follow up CT of the head in October 2013 showed no significant interval change. (Fig. 5,6)

Figure 5 - CT of head October 7, 2013- coronal plane

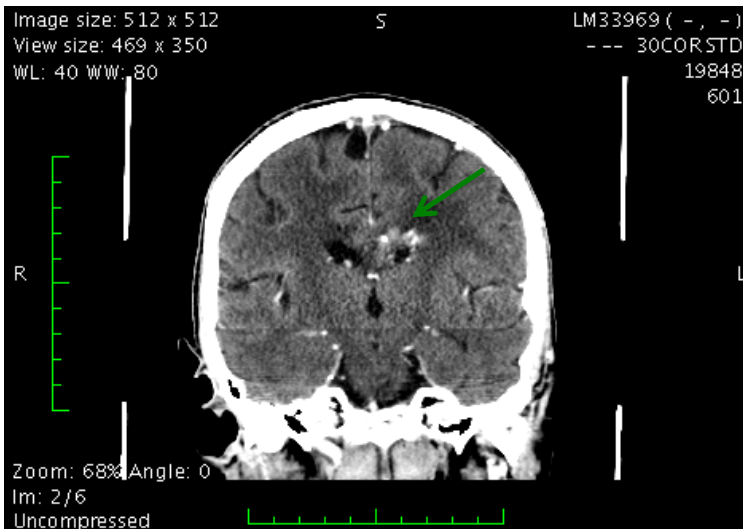
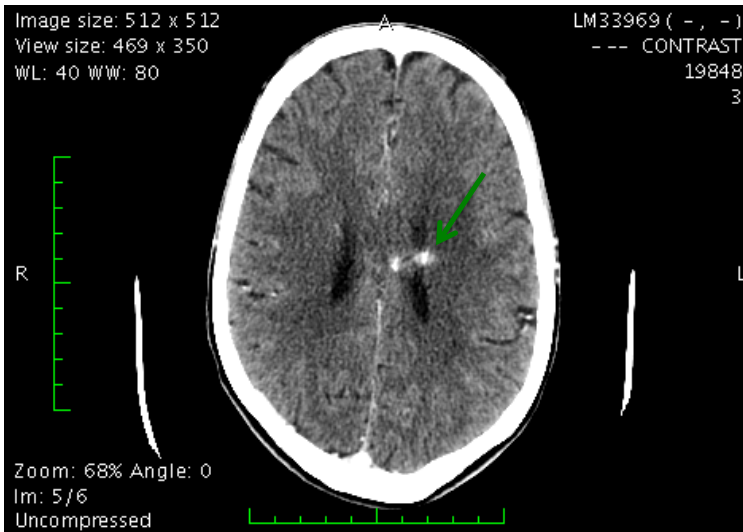


Figure 6 - CT of head October 7, 2013- transverse plane



A follow up CT of the head in April 2014 showed no interval change, and no evidence of tumor recurrence. (Fig. 7,8).

Figure 7. - CT scan of head April 17, 2014 - coronal plane

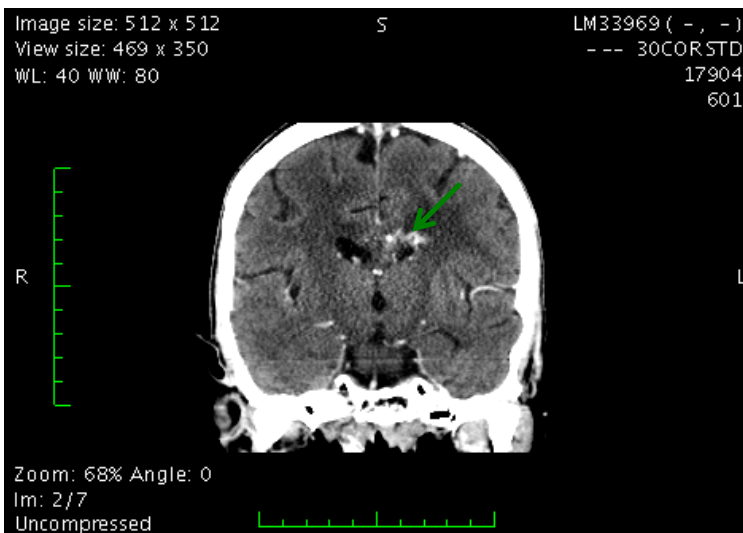
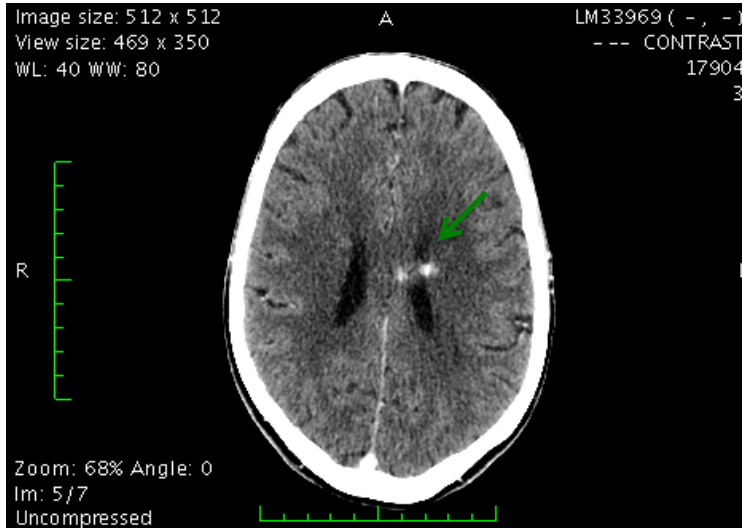


Figure 8. - CT scan of head April 17, 2014 - transverse plane



During a follow up consultation on September 4, 2014, approximately 3 ½ years from diagnosis, P.S. showed a clinical improvement of his previous symptoms. There was no evidence of paresthesia. Sensory and motor function improved, as did short-term memory with no apparent changes in personality. Judging from the imaging, laboratory results, and his signs and symptoms, his clinical course from the start of the treatment at IHC showed no remaining evidence of disease, with no progression to other sites of the brain. His most recent follow up was on May 26, 2015. Symptomatically, he continues to do well, and the most recent head CT from May 2015 reported no interval change and no evidence of recurrent tumor (Fig 9, 10).

Figure 9. - CT scan of head - May 7, 2015 - coronal plane

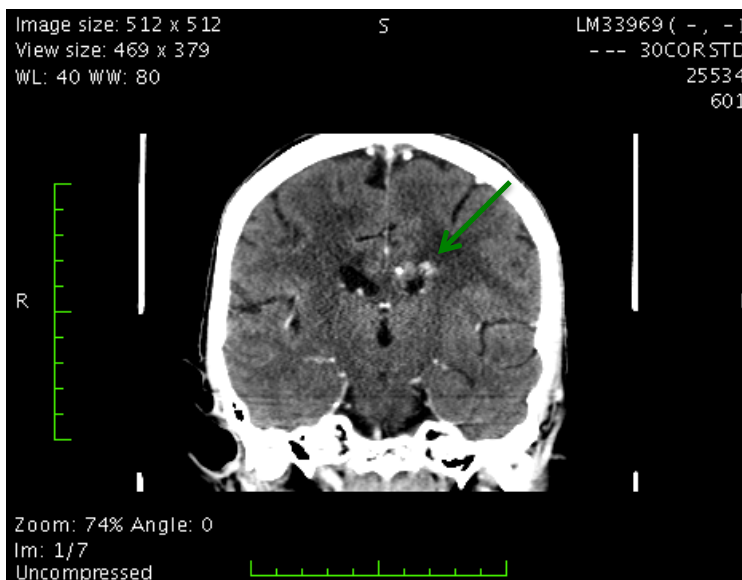
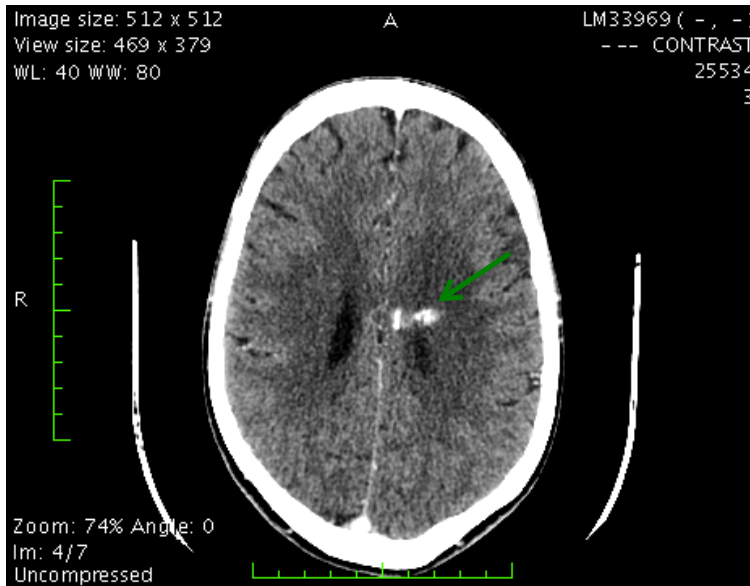


Figure 10. - CT scan of head – May 7, 2015 – transverse plane



P.S. remains on his prescribed oral targeted supplementation regimen for the past 4.5 years, including DCA at 20 mg/Kg daily in 2 divided doses (5 days on, 2 days off), Boswellia serrata 333 mg/capsule p.o. BID, Can-Arrest 1 capsule p.o. BID (curcumin 200 mg, boswellia 200 mg, quercetin 100mg), WobenzymeN 3 tablets p.o. TID, and melatonin 10mg p.o. h.s. He continues to tolerate these well, with no reported side effects, now almost 5 years from diagnosis.

Discussion:

Glioblastoma multiforme (GBM) is the most frequent and most aggressive brain tumor in adults. The introduction of TMZ has advanced treatment strategies for malignant gliomas. There is tremendous variability on the survival benefit of adjunct chemoradiation for malignant gliomas, which may be partly explained by genomic molecular alterations. For example, in a large randomized trial comparing radiation alone and radiation alongside TMZ in GBM patients, 2 year overall survival was 49% for those with MGMT methylated tumors compared to 15% in individuals with unmethylated MGMT tumors^{20,21}. Given the considerable number of GBM cases who are refractory to radiation alone or in combination with TMZ, the need for additional effective therapeutic options are overwhelming²². Currently, survival with standard therapy incorporating surgery, cranial irradiation, and TMZ remains unacceptably poor including fewer than 10% of patients surviving 5 years after diagnosis²³. Despite notable technical advances in both the surgical and radiotherapeutic treatment approaches to malignant gliomas during the last decade,

patient survival has not improved. The presence of hypoxic tumour cells is thought to be a major reason for tumour resistance to radiotherapy²⁴. Many cytotoxic chemotherapeutic drugs mediate their effects in part by stimulating anti-tumor immunity. With the increasing appreciation of the role of immune system in cancer treatment, there is a growing interest in the potential of local tumor hyperthermia to activate anti-tumor immune responses²⁵. When cancer cells are subjected to high temperatures, between the range of 40 and 43°C, the majority of cancer cells tend to undergo apoptosis, while the majority of healthy cells tend to survive²⁶. Malignant cells differ in morphology from normal cells. Tumor architecture and vasculature supply is more chaotic, leading to an immature, structurally defective microvascular system that is less resilient to perfusion shifts. Heat increases membrane fluidity and instability of cancer cells leading to cell death directly or indirectly through increased delivery of cytostatic chemotherapy. Heat shock induces expression of p53, a tumor suppressor transcription factor that is mutated in cancer cells. In addition, heat induces protective anti-tumor immune responses by presenting tumor peptides to naïve T-cells. Lymphocytes will mature and proliferate into cytotoxic T lymphocytes and CD4+ helper cells, mounting an adaptive immune response³. The use of heat treatment in association with TMZ is feasible and quadruple treatment (surgery, chemotherapy, conformal radiotherapy and hyperthermia) represents a promising new approach to the treatment of GBM²⁷. This case report shows the safety and efficacy of integrative oncology treatments for GBM. The long-term progress of the patient clearly shows the benefit of hyperthermia used in conjunction with conventional therapy.

Conclusion

Brain tumors present a unique characteristic different from the usual tumors of the body primarily because of the potential life threatening neurological complications. This case report shows that integrative oncology treatment is safe and effective for the management of GBM. The use of naturopathic treatment played an important role for the patient's wellness and quality of life. Hyperthermia in combination with targeted supplementation has shown to be effective in the management of GBM with fewer side effects when compared to standard conventional therapy alone.

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