# Ketogenic metabolic therapy in conjunction with standard treatment for glioblastoma: A case report

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**Abstract.** Glioblastoma (GBM) is the most common primary malignant brain tumour in adults. The standard of care consists of surgical resection and concurrent chemoradiation, followed by adjuvant temozolomide chemotherapy. This protocol is associated with a median survival of 12-15 months, and <5% of patients survive >3 years. Ketogenic metabolic therapy (KMT) targets cancer cell metabolism by restricting glucose availability and evoking differential stress resistance and sensitization, which may augment the standard treatments and lead to therapeutic benefit. The present study reports the case of a 64-year-old woman with isocitrate dehydrogenase (IDH)-wildtype GBM who pursued the standard treatment protocol in conjunction with an intensive, multimodal KMT program for 3 years. The KMT program consisted of a series of prolonged (7-day, fluid-only) fasts, which were specifically timed to maximize the tolerability and efficacy of the standard treatments, combined with a time-restricted ketogenic diet on all other days. During the first and second treatment years the patient sustained a glucose ketone index (GKI) of 1.65 and 2.02, respectively, which coincided with complete clinical improvement, a healthy body-mass index and a high quality of life, with no visible progressive tumour detected on imaging at the end of the second year. In the setting of the death of an immediate family member leading to increased life stress, slightly relaxed KMT adherence, and a higher GKI of 3.20, slow cancer progression occurred during the third year. The adverse effects attributed to KMT were mild. Despite the limitations of this case report, it highlights the feasibility of implementing the standard treatment protocol for GBM in conjunction with an intensive, long-term, multimodal and specifically timed KMT program, the potential therapeutic efficacy of which may depend upon achieving as low a GKI as possible.

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## Introduction

Glioblastoma (GBM) is the most common primary malignant brain tumour in adults and among the most lethal of human cancers (1). Treatment of GBM is challenging due to its highly infiltrative nature, broad range of genetic heterogeneity, and ability to establish an immunologically 'cold' microenvironment (2). The standard of care consists of maximal surgical resection and 6 weeks of concomitant radiation and temozolomide chemotherapy, followed by six 5-day cycles of adjuvant temozolomide given every 28 days (3). Outside of well-selected patients in clinical trials, this protocol is associated with a median survival of 12 to 15 months (4,5). Fewer than 5% of GBM patients survive for longer than 3 years and are known as 'long-term survivors' (6,7).

Cancer cells exhibit altered cell metabolism and impaired mitochondrial biology (8,9). A widespread feature of cancer cell metabolism is the Warburg effect, which refers to a dramatic increase in the aerobic fermentation of glucose that may act to compensate for damaged cell respiration through the generation of fermentation energy (10). Another potential compensatory mechanism is the Q-Effect, which involves a rewiring of glutamine metabolism to generate fermentation energy (11). Cancer cells also rely on increased growth signalling pathways involving insulin, insulin-like growth factor-1 (IGF-1), and mammalian target of rapamycin (mTOR) (12,13). Beyond these alterations, there is evidence of impaired mitochondrial biology in human gliomas, including GBM (14). Glioma cells show a reduced mitochondria content (15), a low frequency of fusion and fission (16), and a plethora of mitochondrial DNA mutations (17,18). Moreover, GBM mitochondria display a 56-92% reduction in the activities of respiratory chain complexes I to IV (19), increased oxidative damage (20), and frequent swelling and cristolysis (16,20).

Given the metabolic and mitochondrial profile of GBM, the standard treatment protocol may benefit from ketogenic metabolic therapy (KMT) (21). Common strategies include fasting and ketogenic diet regimens, which restrict glucose availability and generate fat-derived ketones leading to a lowered blood glucose-to-ketone (beta-hydroxybutyrate) ratio, or glucose ketone index (GKI) (22). Lowering the GKI

also evokes differential stress resistance and sensitization, with normal cells showing enhanced resistance to stressors (including radiation and chemotherapy), whereas cancer cells are sensitized (23). Beyond lowering the GKI, KMT tempers insulin, IGF-1, and mTOR availability (12,24). Moreover, KMT increases the efficiency of ATP production, decreases oxidative stress, and stimulates mitogenesis and mitophagy. Despite these theoretical advantages, supportive interventional evidence in patients with GBM remains limited (25). Only one study has incorporated a combined fasting and ketogenic diet protocol in a rigorous manner (26). This study showed that an intensive, combined KMT program was feasible and safe in patients with GBM. However, it did not specifically time KMT with the standard treatments to take advantage of differential stress resistance and sensitization.

Given the collective evidence, we hypothesized that applying the standard treatment protocol in conjunction with an intensive, long-term, multimodal KMT program, specifically timed to maximize the tolerability and efficacy of the standard treatments, would be feasible and potentially beneficial for survival in a patient with GBM.

## Case report

We report the case of a 64-year-old female teacher of European background who attended Rotorua Hospital (Rotorua, New Zealand) in December 2020 with 2 days of left upper and lower limb numbness and weakness. Medical history included hypothyroidism and gastro-oesophageal reflux, for which she was taking levothyroxine and omeprazole. She was a non-smoker and lived with her husband. Magnetic resonance imaging (MRI) brain with contrast revealed a large enhancing mass (33x30x39 mm) in the right parietal lobe with local mass effect. She was transferred to neurosurgery at Waikato Hospital (Hamilton, New Zealand) for surgical resection. Biopsy evaluation revealed areas of pleomorphic cells with brisk mitotic activity, geographic and palisading necrosis, and endothelial proliferation, with immunochemistry showing an isocitrate dehydrogenase (IDH)-wildtype, borderline methylated GBM (average CpG site methylation rate 8.3%) (Fig. 1). Post-operative MRI demonstrated no residual enhancing tumour and she was discharged home on tapering dexamethasone. She was reviewed by oncology as an outpatient and planned for 6 weeks of concomitant radiation therapy (60 Gy in 30 fractions) and temozolomide (75 mg/m$^2$ daily), followed by six cycles of adjuvant temozolomide (150 mg/m$^2$ daily on cycle 1, increasing to 200 mg/m$^2$ daily for cycles 2-5). The treating oncologist also referred her to a neurologist for consideration of KMT.

Upon review by neurology, the only residual neurological symptom was mild left lower limb weakness. Our patient measured 166 cm in height and 77.5 kg in weight, resulting in an overweight body-mass index of 28.1 kg/m$^2$. She had an Eastern Cooperative Oncology Group (ECOG) score of 1, with 5-/5 power in all left lower limb movements. Following the assessment, she was given the option of a KMT protocol that incorporated prolonged fasting, time-restricted feeding, and a modified ketogenic diet in a manner intended to maximize the tolerability and efficacy of the standard treatments (Fig. 2). The prolonged fasts consisted of eight 7-day, fluid-only (water, tea, or coffee) fasts, with the first fast commencing 4 days prior to chemoradiation, the second fast occurring in the third week of chemoradiation, and the latter six fasts commencing 4 days prior to each cycle of temozolomide. On all other days, she was instructed to undergo a time-restricted ketogenic diet (TRKD), which involved reducing feeding times to two meals per day, with no food intake in the intervening hours. She could choose the timing of the two meals every day and was permitted 1 h per meal to ensure that food intake was restricted to 2 h per day, with the remaining 22 h dedicated to fasting. All meals consisted of a modified ketogenic diet, which was 60% fat, 30% protein, 5% fibre, and 5% net carbohydrate by weight and comprised of whole foods (green vegetables, meats, eggs, nuts, seeds, creams, and natural oils). She was instructed to eat until satiated. Written informed consent was obtained and a booklet provided with guidelines, recipes, and space to record daily (bedtime) blood glucose and ketone levels, which she measured using a blood glucose and ketone monitor (CareSens Dual, Pharmaco Diabetes, Auckland, New Zealand). The lead investigator provided regular email support.

Our patient pursued the standard treatments alongside KMT for 3 years, during which we documented her blood glucose and ketone levels (± standard deviation) in a spreadsheet (Table SI). We used this data to calculate her mean GKI, which we plotted alongside the tumour features on imaging (Fig. 3). She commenced her chemoradiation therapy approximately 6 weeks after symptom onset (4 weeks after surgery).

During the first and second treatment years, our patient maintained a low GKI, clinically improved, and there were no signs of cancer progression on imaging. In the first year, her average weekly blood glucose level was 4.65 ± 0.38 mmol/l and her blood ketone level was 2.82 ± 1.43 mmol/l, resulting in a GKI of 1.65 (ranging from 0.52 to 5.97 during any week). In the second year, her average blood glucose level was 4.68 ± 0.19 mmol/l and her blood ketone level was 2.32 ± 0.67 mmol/l, resulting in a GKI of 2.02 (range, 1.16 to 5.38). Clinically, her mild left lower limb weakness resolved, leading to an ECOG score of 0 by month 6. Her weight decreased to 56.4 kg (27% reduction from baseline), resulting in a normal body-mass index of 20.5 kg/m$^2$ by month 6. Serial MRIs revealed no visible tumour from month 4 onwards. The ECOG, BMI, and MRI measurements remained stable until the end of the second treatment year, without any clinical or radiological evidence of cancer progression.

Entering the third treatment year, our patient experienced the death of an immediate family member, which led to several weeks of dramatically increased life stress and poor sleep followed by a slight relaxation of KMT, clinical decline, and radiological features concerning for cancer progression. Her average weekly blood glucose level was 5.24 ± 0.62 mmol/l and her blood ketone level was 1.64 ± 0.65 mmol/l throughout the year, resulting in a GKI of 3.20 (range, 1.14 to 17.20). Although she remained clinically stable, MRI at the end of month 26 showed a small new enhancing focus in the resection bed considered to represent possible cancer progression. Monitoring with serial MRIs demonstrated a significant change of this enhancing focus, which increased in size from 5 mm to 20 mm over 8 weeks. This prompted a repeat resection in month 29. Biopsy evaluation revealed areas of pleomorphic

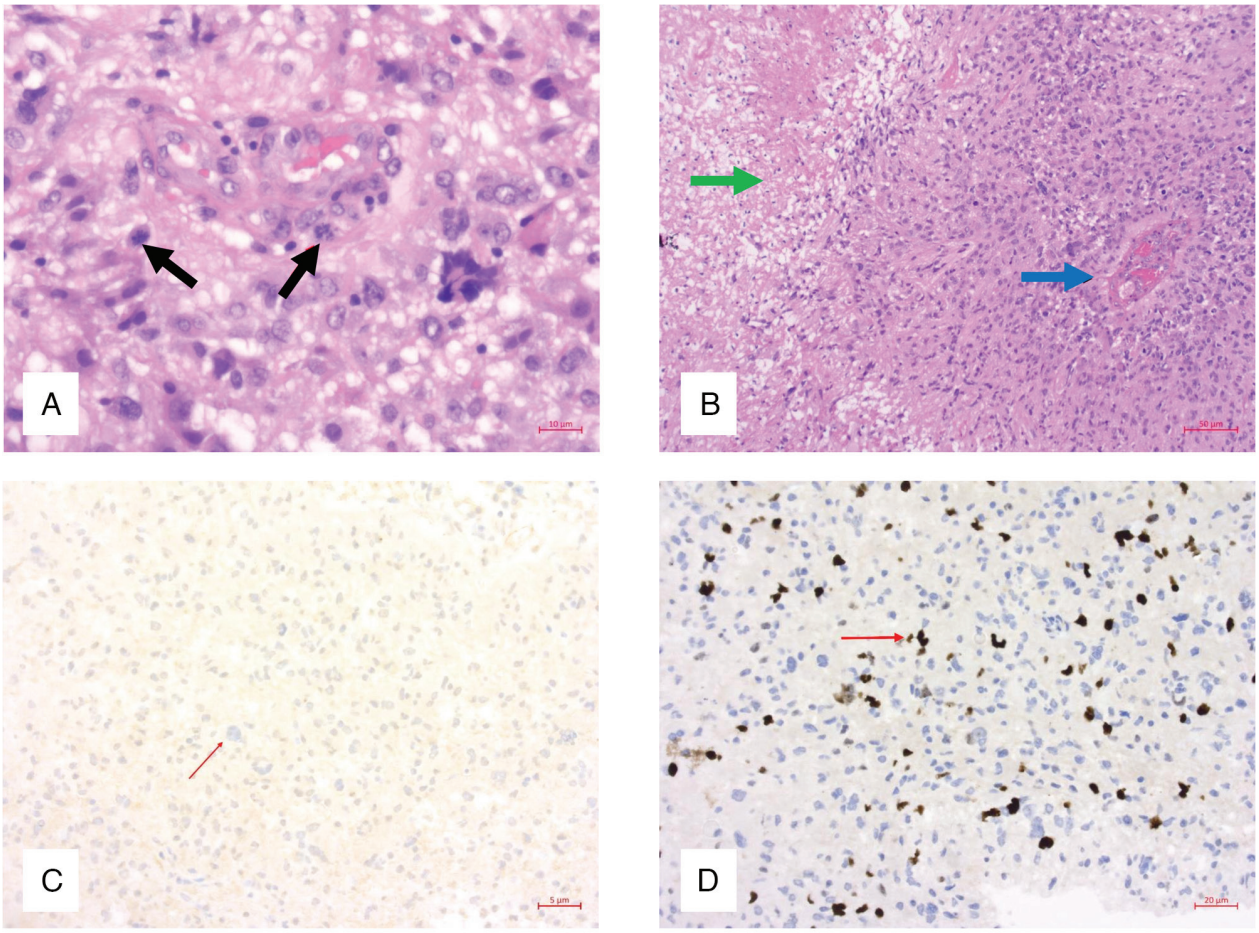


Figure 1. Brain biopsy histological images. (A) H&E stain, showing pleomorphic cells with brisk mitotic activity (black arrows). (B) H&E stain, showing areas of necrosis (green arrow) and endothelial proliferation (blue arrow). (C) Immunohistochemistry, showing negative IDH-1 (R132H) status (small red arrow) and (D) immunohistochemistry, showing a high Ki-67 proliferation index (small red arrow). H&E, haematoxylin and eosin; IDH, isocitrate dehydrogenase; Ki-67, antigen Kiel 67.

cells, necrosis, and hyalinized blood vessels consistent with previous radiation therapy, with immunochemistry showing an IDH-wildtype, unmethylated GBM (average CpG site methylation rate of 2.5%). Following surgery, our patient retained 3/5 power in the left upper limb and 1/5 power in the left lower limb, neither of which recovered in the following weeks, leading to a persisting ECOG score of 2 and the gradual emergence of depressive symptoms. Post-operative MRI demonstrated several small enhancing foci bordering the surgical cavity, the largest of which measured 10 mm, consistent with residual tumour. She was commenced on dexamethasone 4 mg daily and underwent a further 2 weeks of radiation therapy (35 Gy in 10 fractions). Despite this regimen, MRI in month 33 showed an increase in the size of the enhancing mass within the primary resection cavity with associated mass effect. Due to the ongoing weakness and imaging findings, dexamethasone was increased to 8 mg daily and remained at a variable dose of 4 to 16 mg daily from months 30 to 36, during which the GKI increased to 4.07. Weight increased during this time to 68.0 kg, resulting in a body-mass index of 24.7 kg/m$^2$ by month 36. MRI in month 35 showed an increase in size and avidity of the enhancing mass, a new small enhancing nodule involving the contralateral splenium, and progressive non-enhancing white matter changes. These findings were considered to represent tumour progression. Second-line systemic options such as bevacizumab combined with irinotecan chemotherapy were discussed with our patient, but she declined due to financial constraints and opted for best supportive care.

There were several adverse effects during treatment. Adverse effects attributed to chemoradiation by our patient and her oncologists included mild fatigue, headache, and alopecia. Adverse effects attributed to adjuvant temozolomide included nausea and a low platelet count of 45,000 $\mu$l after cycle 3, which resulted in a 12-week break from chemotherapy and a dose reduction to 200 mg temozolomide for the last three cycles, followed by resolution of the nausea and low platelet count. Adverse effects attributed to the prolonged fasts included mild fatigue, diarrhoea, and cold intolerance. No significant adverse effects were attributed to the TRKD, although our patient and her family found it to be a significant commitment. Positive effects attributed to KMT included reduced chronic neck, back, and bilateral shoulder pain. Our patient also experienced a general feeling of well-being until she lost her functional independence following the second surgical resection. Moreover, she found KMT to be inexpensive compared with further systemic options, which were cost-prohibitive.

Coming into the fourth year, in the setting of her ongoing post-surgical weakness and subsequent depression, our patient

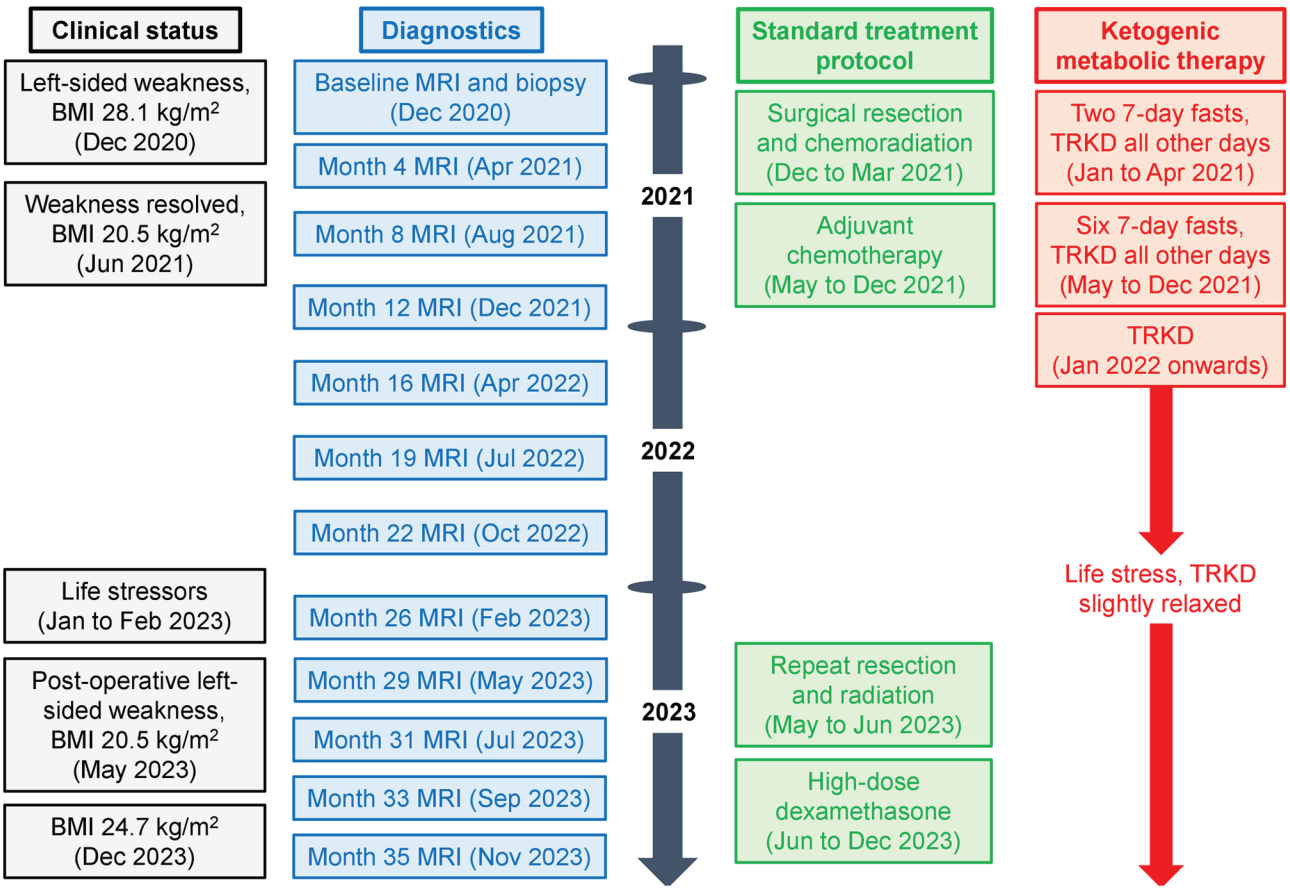


Figure 2. Patient timeline. BMI, body-mass index; MRI, magnetic resonance imaging; TRKD, time-restricted ketogenic diet.

opted to significantly relax her KMT adherence, which subsequently led to a rapid and progressive clinical decline. She passed away 6 weeks later, during month 38.

## Discussion

This case study is novel in that a patient with IDH-wildtype GBM pursued the standard of care (surgery, chemoradiation, adjuvant temozolomide) in conjunction with an intensive, long-term, multimodal KMT program (prolonged fasting, time-restricted feeding, ketogenic diet), which was specifically timed to maximize the tolerability and efficacy of the standard treatments. By the end of the second treatment year, she achieved a complete clinical improvement, a stable body-mass index in the healthy range, and a high quality of life, with no signs of cancer progression on imaging. During the third year, following a period of dramatically increased life stress and a slight relaxation of KMT adherence, slow cancer progression occurred. Although the KMT program required a significant commitment, adverse effects were mild.

Given their differing mechanisms, integrating the standard treatments with KMT can lead to synergistic therapeutic effects in cancer (23). Broadly speaking, surgery, radiation, and chemotherapy are designed to target and eliminate cancer cells by directly removing tumour bulk and damaging DNA to induce cytotoxicity (27). Rather than directly eliminating cancer cells, KMT is designed to reinforce the resistance of normal cells to radiation and chemotherapy by depriving them of nutrients, which diverts energy and resources into maintenance and repair processes (28). By contrast, since cancer cells cannot slow their growth due to the uncontrolled activation of growth pathways and mutations in tumour suppressor genes (29), KMT may enhance the sensitivity of these cells to the standard treatments by restricting their access to glucose and growth factors (28). We attempted to maximize the tolerability and efficacy of the standard GBM treatments by administering KMT in a 'press-pulse' manner, which is designed to induce a chronic, low-grade stress on cancer cell metabolism (the 'press') that is capitalized upon by a more acute, high-grade stress (the 'pulse') (30). In our patient, the press consisted of the TRKD, whereas the pulse was comprised of the prolonged fasts, which were additionally timed to maximize differential stress resistance and sensitization to the standard treatments (23). The administration of press-pulse KMT may have contributed to the long-term survival experienced by our patient.

Evidence from interventional studies in animals and humans indicates that lower GKIs lead to more effective growth suppression in brain tumours. In animal models of astrocytoma and glioma, a GKI <6 in combination with radiation or chemotherapy leads to lower brain tumour volumes and increased survival (22). Although the human evidence is not as robust, several case reports have indicated that intensive KMT may suppress cancer growth in grade 4 astrocytoma and GBM, whereas a loosening of KMT can facilitate progression (31-33). Similarly, our patient's KMT adherence and GKI status

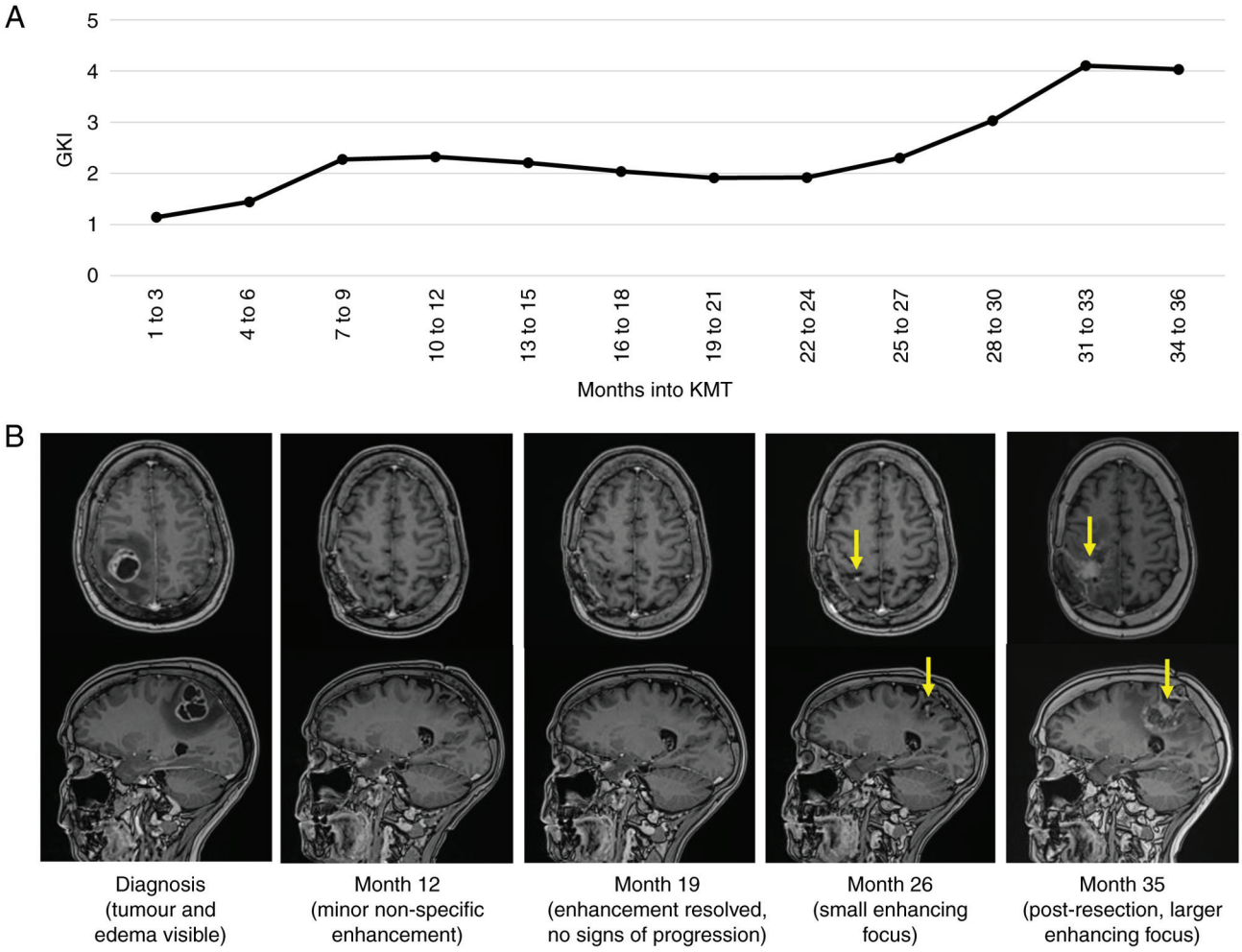


Figure 3. Temporal association between (A) mean 3-monthly GKIs and (B) tumour imaging features during 3 years of KMT (yellow arrows indicate areas of enhancement). GKIs, glucose ketone indices; KMT, ketogenic metabolic therapy.

broadly correlated with the behaviour of her tumour. During the first and second treatment years, she received the standard treatment protocol while sustaining a GKI of 1.65 and 2.02, respectively, which coincided with clinical improvement and no visible tumour on imaging. Entering the third treatment year, she slightly relaxed her adherence and sustained a GKI of 3.20, which coincided with slow radiological progression of the tumour. As this is a case study, we cannot draw conclusions regarding the initial focus of cancer progression. However, one possibility is that tight adherence to the TRKD in the second year helped suppress the growth of the tumour, whereas the relaxed adherence in the third year contributed to (slow) progression. The weekly GKI ranged as high as 17.20 during the third year, which resulted from a combination of hyperglycaemia and hypoketonemia. Importantly, this value was far higher than the maximal GKI measured in either of the previous treatment years, which indicates that sustaining a consistently low GKI, with minimal variability, may be important. Alternatively, it is possible that the slight relaxation in adherence was not clinically relevant and that the TRKD 'press' on its own was unable to halt tumour growth. Given the latter possibility, long-term GBM suppression in some patients might require additional 'pulses' of prolonged fasting alongside further radiation, chemotherapy, or metabolic drugs such as glutamine blockers (11). Regardless of mechanism, since it has been suggested that dexamethasone compromises survival in GBM (34), which occurs in part through elevated blood glucose levels (35), the administration of high daily doses of this drug may have blunted the potential therapeutic efficacy of the KMT program during the latter half of the third year.

During the first and second treatment years, our patient experienced substantial weight loss (27% of her initial body weight). This technically represents a CTCAE grade 3 event. However, it is crucial to recognize that she was initially overweight, her weight loss was intentional, and her body-mass index stabilized within a healthy range. While unintentional weight loss can precipitate sarcopenia and cachexia in patients with advanced cancer, intentional weight loss is associated with a lower risk of many types of cancer (36,37). Moreover, when correctly executed, fasting and ketogenic diet protocols can comfortably meet a patient's nutritional needs while exerting a sparing effect on lean mass (38), with some studies indicating that ketogenic diets induce weight gain in cancer patients with cachexia (39). Furthermore, several case reports involving KMT have shown that significant intentional weight loss (up to 28% of initial body weight) can be associated with positive outcomes in patients with GBM and other advanced cancers (31,32,40,41).

We cannot draw firm conclusions with respect to the mechanism of KMT in our patient, or its impact on her long-term survival. With respect to mechanism, a potential weakness of our KMT program is that it did not specifically target glutamine, which may also be utilized as a fermentable fuel in GBM (11). Since prolonged fasting reduces the activity of glutaminase, which catalyses the conversion of glutamine to glutamate as an energy source for the TCA cycle (42), the prolonged fasts may have non-specifically lowered glutamine availability; however, the addition of a glutaminase inhibitor, such as 6-diazo-5-oxo-L-norleucine (DON), would probably be more effective (43). Beyond DON, it is also possible that our patient's KMT could have been augmented by incorporating drugs that can alter metabolism and have been associated with improved cancer outcomes, such as metformin, which can suppress gluconeogenesis (44), and atorvastatin, which may enhance ketogenesis (45,46). With respect to the potential impact of KMT on survival, the long-term survivor status experienced by our patient is in keeping with preliminary findings from other studies that have investigated KMT in glioma patients (47). However, it is important to point out that our patient displayed several positive prognostic features such as her gender, complete resection, and borderline methylation status (48), all of which may have contributed to her long-term survival.

In conclusion, this case study is novel in that a patient with IDH-wildtype GBM pursued the standard of care in conjunction with an intensive, long-term, multimodal KMT program, which was specifically timed to maximize the tolerability and efficacy of the standard treatments. By the end of the second treatment year, she achieved complete clinical improvement, a healthy body-mass index, and a high quality of life, with no visible progressive tumour detected on imaging. In the setting of dramatically increased life stress and slightly relaxed KMT adherence, slow cancer progression occurred during the third year. Adverse effects attributed to KMT were mild. Despite the limitations of this case study, it highlights the feasibility of implementing the standard treatment protocol in conjunction with an intensive, long-term, multimodal, and specifically timed KMT program, the potential therapeutic efficacy of which may depend upon achieving as low a GKI as possible.

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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**

MCLP contributed to the conceptualization, design, analysis, and writing of both the original and subsequent drafts. PHD, ZT, FZ and BJM contributed to data collection, and reviewed and edited the manuscript. MCLP and BJM confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

**Ethics approval and consent for participation**

Ethics approval was not required for this study in accordance with our local and institutional requirements. The study was conducted in accordance with local legislation and institutional requirements. The participant provided written informed consent to participate in this study.

**Patient consent for publication**

Written informed consent for publication of this article was obtained from the participant.

**Competing interests**

The authors declare that they have no competing interests.

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