

Tumor regression following autologous tumor lysate–loaded dendritic cell vaccination immunotherapy: illustrative case

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BACKGROUND Despite years of research, the standard of care (SOC) treatment for grade 4 glioma has remained virtually unchanged for the last 2 decades. Autologous tumor lysate–loaded dendritic cell vaccination (DCVax-L), a novel immunotherapy, has demonstrated a significant survival benefit in a phase 3 trial.

OBSERVATIONS A 34-year-old male presented with episodes of lightheadedness and was subsequently diagnosed with a large fronto-insulo-temporal tumor, likely to be high grade. He underwent an asleep craniotomy for debulking, with a residual tumor noted in the frontal lobe and amygdala. Tumor histopathology was reported as isocitrate dehydrogenase (IDH) mutant methylated grade 4 astrocytoma. He received SOC treatment, alongside a course of DCVax-L. Surveillance imaging showed cystic transformation followed by a reduction in size of the residual tumor in the frontal lobe; the residual in the amygdala had regressed entirely. The patient remained clinically well and had returned to his preoperative functionality.

LESSONS The authors report a patient with grade 4 astrocytoma who received DCVax-L treatment in addition to SOC adjuvant therapy. The pattern and extent of tumor regression are highly unusual and atypical for what is seen or expected with adjuvant SOC treatment alone. The addition of DCVax-L to SOC opens new avenues in the management of this difficult disease.

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KEYWORDS tumor regression; glioblastoma; DCVax-L; immunotherapy; treatment; case report

Glioblastoma multiforme (GBM) is the most common malignant primary central nervous system (CNS) tumor, accounting for 16% of all primary CNS tumors and 54% of all gliomas.¹ GBM is highly aggressive, with a median survival of 15–17 months and a 5-year survival rate of 5%.² Despite decades of research into therapeutic options for GBM, recurrence rates continue to be dismally high at 90%, with the tumor typically recurring within 6–8 months.³ GBMs with certain molecular markers, such as O⁶-methylguanine-DNA-methyltransferase methylation or isocitrate dehydrogenase (IDH) mutation, are known to confer a slightly more favorable prognosis, with the presence of the latter now referred to as “IDH-mutant grade 4 astrocytoma” in the 5th edition update of the World Health Organization (WHO) classification of CNS tumors.⁴

The standard of care (SOC) treatment for grade 4 gliomas, in general, is gross-total resection, postoperative radiotherapy to 60 Gy in 30 fractions with concomitant temozolomide, followed by adjuvant temozolomide chemotherapy.⁵ This has remained virtually unchanged for almost 2 decades because of the lack of novel treatment options.^{6,7} An

important emerging therapeutic approach for these tumors includes the use of immunotherapy, whereby autologous tumor lysate–loaded dendritic cell vaccination (DCVax-L), in particular, has shown significant promise.⁸ Here, we report the case of a patient who underwent DCVax-L treatment at our center.

Illustrative Case

A 34-year-old male, previously fit and well, presented to his general practitioner with multiple episodes of transient lightheadedness, dizziness, and headaches over a 4-month period. He experienced up to 4 episodes daily, which impacted his work and day-to-day activities. His neurological examination at presentation revealed no focal deficits.

He underwent magnetic resonance imaging (MRI) of his brain, which revealed a large heterogeneous enhancing lesion in the right frontotemporal and insular region likely to be a high-grade tumor (Fig. 1). Imaging of his chest, abdomen, and pelvis revealed nothing of note. He was started on dexamethasone and levetiracetam, and

ABBREVIATIONS CNS = central nervous system; DCVax-L = autologous tumor lysate-loaded dendritic cell vaccination; GBM = glioblastoma multiforme; IDH = isocitrate dehydrogenase; MRI = magnetic resonance imaging; SOC = standard of care; WHO = World Health Organization.

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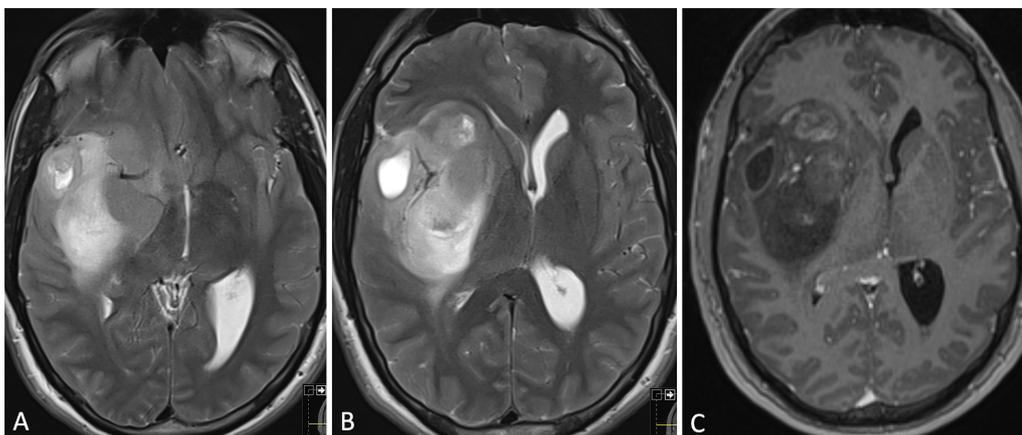


FIG. 1. Axial T2-weighted (A and B) and axial T1-weighted post-gadolinium (C) images show an area of mixed T2 hyperintensity and isointensity with heterogeneous enhancement in the right fronto-insulo-temporal region, corresponding to a high-grade glioma.

a week later, he underwent an asleep right temporoparietal craniotomy for debulking of the right temporal lobe component of the tumor. Postoperative imaging showed residual tumor primarily in the frontal lobe and amygdala (Fig. 2). His postoperative course was uneventful. Histopathology demonstrated a methylated, IDH-mutant astrocytoma (CNS WHO grade 4).

Postoperatively, he received SOC treatment with concomitant radiotherapy and temozolomide, followed by 6 cycles of adjuvant temozolomide (Stupp protocol). He tolerated the chemoradiotherapy well with only fatigue as his primary complaint. He received 3 doses of DCVax-L, on a compassionate basis, as part of his oncological treatment, administered in 3 consecutive weekly doses. There were no other conventional treatments, although he did use a range of off-label medications and daily supplements (Table 1). He continued with surveillance MRI. After 3 cycles of temozolomide, MRI showed a non-enhancing cyst-like area in the right frontal lobe where residual tumor had been noted previously (Fig. 1A), while the residual tumor component in the amygdala had regressed entirely (Fig. 3B). At 1 year

postoperatively, the cystic area had further reduced in size since the previous study with no evidence of recurrence (Fig. 4). The patient reported that he was clinically well and had since returned to preoperative functionality and worked at a full-time capacity.

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Observations

GBM, depending on the IDH mutation status, could be classified into either IDH-wildtype or IDH-mutant GBM.⁹ Reflecting the current increased understanding of the importance of IDH mutation in the pathogenesis and subsequent prognosis of gliomas, GBMs that are IDH-mutant are now referred to as IDH-mutant grade 4 astrocytomas since the 2021 update of the WHO classification of CNS tumors.^{4,10} Despite slightly more favorable disease outcomes as compared to those for IDH-wildtype GBMs, IDH-mutant grade 4 astrocytomas are still considered malignant, incurable tumors with aggressive behavior and a median survival of around 30 months.¹⁰ IDH-mutant GBM or

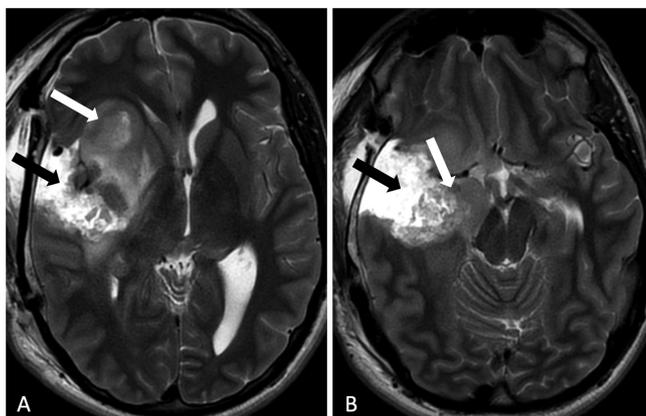


FIG. 2. Axial T2-weighted images (A and B) show a resection cavity (black arrows) at the site of the previously shown temporal component of the astrocytoma. Residual tumor is evident mainly in the frontal lobe and amygdala (white arrows).

TABLE 1. List of off-label medications and supplements

Medications	Supplements & Other Treatments		
Metformin	Probiotics	Curcumin	Quercetin
Atorvastatin	Vitamin B	Indole-3-carbinol	Feverfew
Mebendazole	Milk thistle	EGCG	Pau d'arco
Etodolac	Garlic & oregano	Omega 3	Mistletoe IM
Cimetidine	Papaya leaf	Hydroxychloroquine	Vitamin C IV
Melatonin	Vitamin D	Turkey tail fungi	Artemisinin IV
Valaciclovir	Boswellia	Bromelain	Helleborus IV
Niclosamide	Magnesium	Broccoli extract	Curcumin IV
	Zinc	Red clover	Hyperbaric oxygen
	Lycopene	Berberine	

EGCG = epigallocatechin gallate; IV = intravenous; IM = intramuscular.

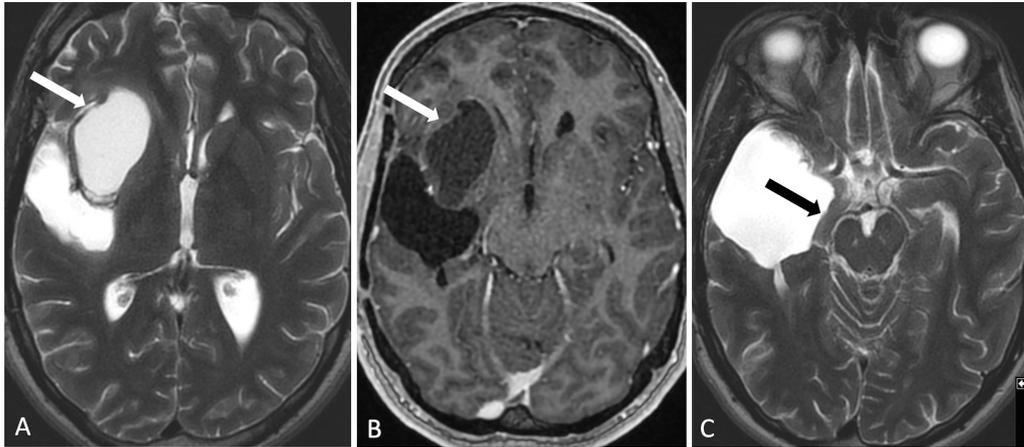


FIG. 3. Axial T2-weighted (A) and T1-weighted post-gadolinium (B) images show a well-defined, homogeneous signal, a non-enhancing cyst-like area in the right frontal lobe anterior to the temporal resection cavity, at the site of the previously shown area of residual tumor (*white arrows*). Axial T2-weighted image more inferiorly (C) the previously shown residual tumor component in the amygdala medial to the resection cavity is also no longer evident (*black arrow*).

grade 4 astrocytoma is more prevalent in the younger cohort than the IDH-wildtype GBM (median age 45 vs 62 years), as exemplified by our patient, and is thought to result from secondary transformation of lower-grade astrocytomas.^{11,12}

Developing an effective treatment for GBM is extremely challenging for a multitude of reasons, one of which is attributed to its inherent heterogeneity, either intratumorally or intertumorally.¹³ Large-scale genomic profiling has demonstrated enormous variability for genetic expression and subtypes across the patient population.¹⁴ In addition, molecular heterogeneity within the tumor itself also poses a challenge because of differing properties and levels of resistance to therapeutic approaches. This has been postulated to contribute to the innate resistance of GBMs to current treatments designed to target specific tumor characteristics, which only eliminate a fraction of tumor cells and eventually fail due to relapse of the remaining unaffected tumor.¹⁵

The Stupp protocol, which is the current SOC treatment, evaluated the addition of concomitant temozolomide during radiotherapy followed by 6 cycles of adjuvant temozolomide.⁵ Stupp et al. demonstrated an increase in median survival by 2.5 months (12.1 vs 14.6 months) and an improved 2-year survival rate (26.5% vs 10.4%) when compared to radiotherapy alone. Since the publication of the protocol in 2005, there have been no further phase 3 clinical trials for systemic treatments that have demonstrated a significant survival benefit for patients with GBM.^{6,7} An exception to this is DCVax-L, where the findings of the phase 3 trial revealed, as compared to external controls, an increased median survival of 2.8 months (19.3 vs 16.5 months) in the overall cohort and 9 months (30.2 vs 21.3 months) in methylated GBMs. The 5-year survival rate more than doubled at 13.7% versus 5% in the external control group.

DCVax-L is a novel immunotherapy treatment that utilizes a patient's own tumor combined with dendritic cells to mobilize an

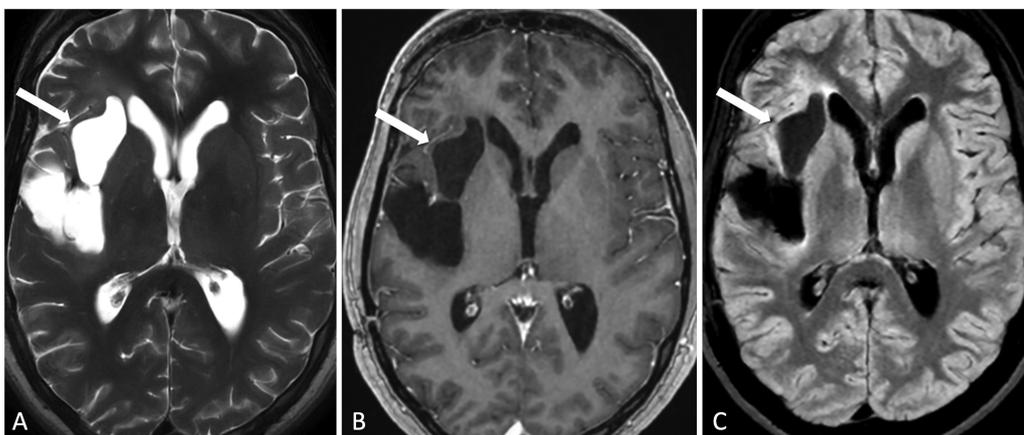


FIG. 4. Axial T2-weighted (A) and T1 post-gadolinium (B) images show a reduction in the size of the well-defined, non-enhancing cystic area in the right frontal lobe (*arrows*) since the previous study. Axial fluid-attenuated inversion recovery image (C) demonstrates signal suppression of the contents of this area (*arrow*), confirming its cystic nature. There remains no evidence of tumor recurrence.

antitumor response.⁸ Since the patient's own tumor lysate is used to prime the dendritic cells, this addresses the aforementioned heterogeneity of GBMs, making it possible to target the spectrum of antigens present in a patient's tumor. This can also prevent mutational processes from occurring around targeted antigens when only a few antigens are targeted.¹⁶ In addition, using dendritic cells as the antigen delivery vehicle versus other agents can bring about a broader immune response, including vastly diverse T-cell populations.¹⁷ Herein, we report a patient with an IDH-mutant grade 4 astrocytoma who received DCVax-L treatment alongside SOC therapy and subsequently demonstrated significant tumor regression together with a return to preoperative functionality and quality of life. The radiological regression remained stable 1 year after surgery with no evidence of recurrence. The limitation of our report is that the observation is related to a single patient; therefore, it is not possible to establish an absolute causality and generalizability with DCVax-L. The patient also reported taking multiple off-label medications and supplements, which may have played a contributory role in the regression, although such treatments lack any concrete class I evidence for use in glioma patients.

Lessons

We report a patient who demonstrated significant radiological regression of his residual tumor following the administration of SOC adjuvant chemoradiotherapy (Stupp protocol) alongside a course of DCVax-L treatment. The pattern and extent of tumor regression are highly unusual and atypical of what is seen with adjuvant SOC treatment alone, even in IDH-mutant gliomas. The addition of DCVax-L to SOC opens new avenues in the management of this difficult disease.

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Disclosures

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Author Contributions

Conception and design: Kamaludin, Ashkan. Acquisition of data: Kamaludin, Ashkan. Analysis and interpretation of data: all authors. Drafting the article: Kamaludin, Sibtain. Critically revising the article: Kamaludin, Ashkan. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kamaludin. Statistical analysis: Kamaludin. Administrative/technical/material support: Kamaludin, Ashkan. Study supervision: Ashkan.

Supplemental Information

Previous Presentations
This work has been presented as a poster presentation at the Society of British Neurological Surgeons Spring Meeting, April 16–19, 2024, Edinburgh, United Kingdom.

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