

CASE REPORT

Dramatic clinical response in the treatment of small cell glioblastoma multiforme

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Abstract

What is known and objective: Small cell glioblastoma (scGBM) is a rare subtype of primary glioblastoma, which typically behave more aggressively compared with classical glioblastoma (GBMs). They are generally associated with poor responses to treatment, and optimal treatment is not known.

Case summary: We present the case of a 51-year-old woman with scGBM with O⁶-methylguanine DNA methyltransferase (MGMT) promoter methylation, demonstrating an unexpected dramatic clinical response to chemoradiotherapy.

What is new and conclusion: This case highlights that treatment with temozolomide-based chemoradiotherapy is justified in patients with scGBM, despite their poor prognosis. MGMT methylation may be associated with clinical responses.

KEYWORDS

chemoradiotherapy, small cell glioblastoma multiforme, temozolomide

1 | WHAT IS KNOWN AND OBJECTIVES

ScGBM is a rare variant of primary glioblastoma, constituting 10% of all GBMs.¹ ScGBMs behave aggressively compared to classical GBMs, with a median overall survival reported as 11 months.² Molecularly, scGBMs may be isocitrate dehydrogenase (IDH) wild type (WT) and have epidermal growth factor receptor (EGFR) amplification,^{2,3} which is thought to contribute to its aggressiveness.⁴

A review by Takeuchi et al. reported clinical and pathological features of 14 cases of scGBM diagnosed between 2005 and 2015. Ten patients received post-operative radiotherapy (PORT) with temozolomide, one received PORT and platinum doublet chemotherapy (carboplatin and etoposide), and three patients received temozolomide alone. Prognosis was poor, with an overall survival between 5 and 23 months, with no patients surviving over 2 years from diagnosis.⁵ Yadav et al. recently reported a case series of 5

patients with IDH WT scGBM, also demonstrating poor prognosis, with four patients having died between 3–6 months post-diagnosis.⁶ The series was limited by the fact that these patients were unable to complete or receive PORT. The one patient who completed PORT with concurrent and adjuvant temozolomide remained alive 8 months after diagnosis, with a partial response.⁶ This may point at the importance of radiotherapy and alkylating chemotherapy in the management of scGBM.

2 | DETAILS OF THE CASE

A 51-year-old woman presented acutely to hospital in December 2020 with a 1 month history of worsening right lower limb weakness, decreased mobility and balance, and memory decline. This occurred on a background history of a malignant ependymoma

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diagnosed 46 years prior, which had been managed with a subtotal resection, insertion of ventriculoperitoneal shunt, radiotherapy, and chemotherapy, with no evidence of recurrence thereafter. She had previously been independent with activities of daily living, but in the month leading to her presentation, her performance status had deteriorated to an Eastern Co-operative Oncology Group (ECOG) score of 3.

A contrast CT brain demonstrated an infiltrative enhancing left hemispheric lesion involving the basal ganglia and temporal lobe and crossing the midline to the right basal ganglia, with moderate mass effect (Figure 1A). A left-sided posterior fossa meningioma was also seen. An MRI was contraindicated due to the patient having an MRI-incompatible shunt.

The patient was admitted and underwent a stereotactic burr-hole biopsy of this left hemisphere lesion. Histopathology demonstrated features in keeping with a glioblastoma with a scGBM morphology, IDH WT. Further management was discussed at neurosurgical multidisciplinary meetings. Given the eloquent location of the lesion, meaningful debulking could not be safely achieved, and a decision was made to pursue chemoradiotherapy.

At the time of commencing radiotherapy, the patient had been on dexamethasone with no functional improvement. She remained ECOG 3. She was treated with concurrent chemoradiotherapy (34 grays in 10 fractions of radiotherapy, with temozolomide 75 mg/m²). In light of the patient's poor functional status, chemoradiotherapy was administered in the inpatient setting. Clinical improvement was evident soon after commencing treatment, and she was subsequently discharged to a home-based rehabilitation program where she continued to make functional progress.

After completion of chemoradiotherapy, there was marked amelioration in lower limb weakness, mobility, and cognition. An interval CT brain undertaken three weeks after completion of chemoradiotherapy confirmed radiological improvement with improved appearances at the left basal ganglia and temporal lobe with decreased mass effect (Figure 1B).

The degree of clinical and radiological responses was felt to be atypical for GBM, and additional histopathological assessment was performed to clarify the diagnosis. Independent pathology reviews confirmed the diagnosis of a small cell GBM, IDH WT. MGMT promoter methylation was present.

Given the clinical benefit observed and the presence of MGMT methylation, the patient continued adjuvant temozolomide as per the STUPP protocol. She completed six cycles of temozolomide with manageable side effects of nausea. Most recent imaging after completion of temozolomide demonstrated an ongoing sustained partial response radiologically (Figure 1C). Clinically, her functional status, mobility, and cognition have returned to baseline.

Due to the rarity of scGBMs, there is a lack of optimal evidence-based treatment guidelines. Landmark trials leading to standard-of-care STUPP protocol did not analyse patients according to histological subtypes.⁷ Typically, scGBMs are associated with a worse prognosis compared to classic GBM. There is a paucity of strong evidence regarding response rates of scGBMs to traditional chemoradiotherapy.

In this setting, our patient's ongoing significant clinical response and partial radiological response to chemoradiotherapy are unexpected and noteworthy. Furthermore, our patient had several poor prognostic factors in addition to small cell histology, all of which would portend an even worse prognosis: poor baseline functional status, lack of debulking surgery, and consequent treatment with a truncated radiotherapy course. It is likely that she would not have been offered systemic therapy, particularly as an inpatient with an ECOG of 3. Nevertheless, it was offered and she tolerated treatment and demonstrated an excellent clinical and radiological response. Approximately 12 months after diagnosis, she continues to have significantly improved survival and most importantly, quality of life.

It is interesting to note that our patient's response occurred in the presence of MGMT promoter methylation. It is well-established that in typical GBMs, MGMT methylation is an independent predictor of improved overall survival and portends a good response to

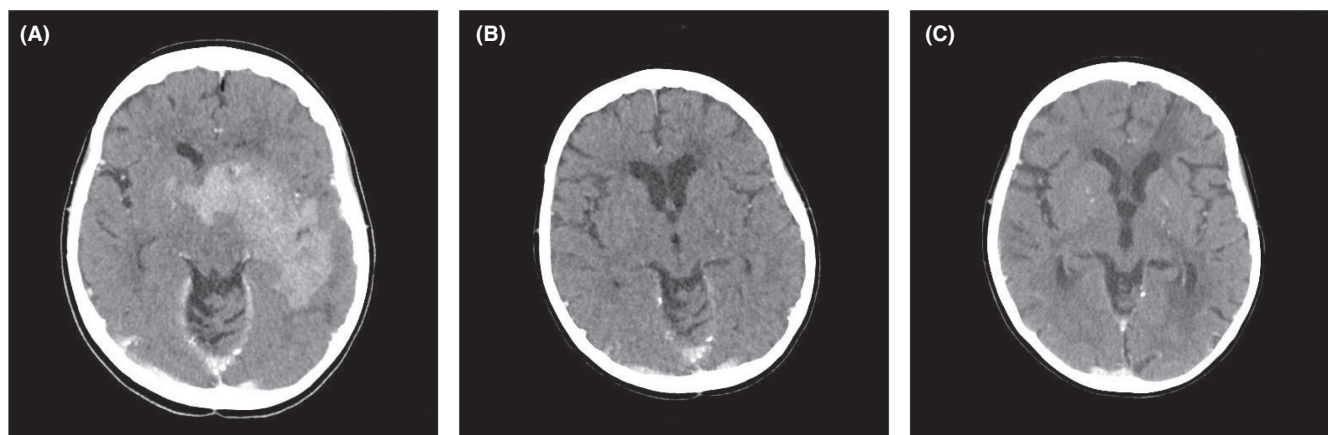


FIGURE 1 CT Brain with contrast pre- and post-treatment with chemoradiotherapy. (A) CT Brain at diagnosis, prior to commencing treatment. (B) CT Brain after completion of chemoradiotherapy. (C) CT Brain after 6 cycles of temozolomide

temozolomide. Mikkelsen et al. found that in IDH WT GBMs, MGMT promoter methylation status is unrelated to histological features, with similar proportions of scGBMs being methylated and unmethylated.⁸ This case may suggest that MGMT promoter methylation negates the poor prognostic effects of a small cell histology and that the same good response to alkylating chemotherapy is seen in this histological subtype.

There are no clear guidelines for further lines of treatment for scGBMs in particular, with most treatments being extrapolated from those used in classic GBMs. Bizu et al. reported a case of a patient with scGBM (IDH1 mutant, MGMT unmethylated) treated with PORT and concurrent temozolomide, with an initial partial response but progressive disease following adjuvant temozolomide, 7 months after diagnosis.⁹ The patient progressed on second-line temozolomide and irinotecan after 3 months and then had rapid progressive disease on third line lomustine. After commencing fourth line bevacizumab and carboplatin and further irradiation, a partial response was seen.⁹ This may reflect that MGMT unmethylated scGBMs have a poorer response to alkylating chemotherapy, though further studies would be needed to confirm this.

This is also the first known case in the literature of a patient with scGBM occurring after a previous ependymoma treated with radiotherapy. It is unclear whether there is a causal association in this case. Nonetheless, it is known that therapeutic radiation, particularly in paediatric populations, is associated with an elevated risk of secondary malignancies, which are typically of higher grades and present at atypical sites.¹⁰

3 | WHAT IS NEW AND CONCLUSION

To our knowledge, the case described is the first to showcase such a dramatic and sustained clinical response to treatment with radiotherapy and temozolomide in scGBM. This case bolsters the notion that a therapeutic trial of temozolomide brings clinical benefit and is thus justified for patients with scGBM, who would otherwise have an extremely poor prognosis. It is possible that MGMT methylation status can be used to help guide clinical decision-making in these cases. This warrants further investigation into the role of MGMT methylation in scGBM, and whether its presence also confers predictive value in this particular histological subtype.

ACKNOWLEDGEMENT

Open access publishing facilitated by Monash University, as part of the Wiley - Monash University agreement via the Council of Australian University Librarians.

CONFLICT OF INTERESTS

None.

PATIENT CONSENT STATEMENT

Written consent for publication of this case report has been obtained from the patient as per institutional guidelines.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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How to cite this article: Zaman FY, McLean C, Ameratunga M. Dramatic clinical response in the treatment of small cell glioblastoma multiforme. *J Clin Pharm Ther.* 2022;47:832-834. doi:[10.1111/jcpt.13608](https://doi.org/10.1111/jcpt.13608)