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# Response to BRAF and MEK1/2 inhibition in a young adult with BRAF V600E mutant epithelioid glioblastoma multiforme: A Case Report and Literature Review

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## ABSTRACT

Epithelioid glioblastoma multiforme (eGBM) is a rare and aggressive variant of glioblastoma multiforme (GBM) that predominantly affects younger patients and can be difficult to distinguish from other gliomas. Data on how patients with eGBM might be best treated are limited, although genomic analyses have shown

*Abbreviations:* 5-ALA, 5-aminolevulinic acid; BRAF, v-Raf murine sarcoma viral oncogene homolog B; CT, computed tomography; e-GBM, epithelioid glioblastoma multiforme; GBM, glioblastoma multiforme; GFAP, glial fibrillary acidic protein; ICH, intracerebral hemorrhage; IDH, isocitrate dehydrogenase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MRI, magnetic resonance imaging; PCV, procarbazine, lomustine (CCNU) and vincristine; PXA, pleomorphic xanthoastrocytoma; TERT, telomerase reverse transcriptase.

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that almost half of tumours harbour activating BRAF gene mutations. Here we present the case of a young female with BRAF V600E-mutant eGBM who had a prolonged response to targeted therapy with the BRAF and MEK1/2 inhibitors dabrafenib and trametinib. We review current knowledge about eGBM, including the emerging role for BRAF- ± MEK1/2- targeted therapy.



ARTICLE INFO

*Keywords:* Epithelioid glioblastoma multiforme; BRAF V600E mutation; targeted therapies; dabrafenib; trametinib

## Introduction

Glioblastoma multiforme (GBM) is the most common primary malignancy of the central nervous system (CNS) seen in adults. Epithelioid glioblastoma multiforme (e-GBM) is a rare and unique histological subtype of GBM which was first characterized in the World Health Organization (WHO) Classification in 2016.[1] This tumor tends to affect younger individuals and exhibits a more aggressive disease course. Overall survival, in general, remains poor (range: ~1-10 months; median: 6 months), and there is a propensity for leptomeningeal dissemination and early recurrence after primary treatment.[2,3] Radiologically, depending on the anatomical location, e-GBMs can resemble meningiomas, metastatic disease and lymphoma.[4] Histopathologically, e-GBMs are usually comprised of tightly packed epithelioid cells, and can be difficult to morphologically distinguish from other gliomas, notably anaplastic pleomorphic xanthroastrocytoma and rhabdoid glioblastoma.[5]

Our knowledge of the clinical course and treatment outcomes for patients with e-GBM is limited to case reports or case series. Current management strategies aim to treat patients as per GBM in general, with the standard of care being maximal surgical resection with adjuvant chemotherapy and radiotherapy (60Gy of fractionated radiotherapy with concomitant and "adjuvant" temozolomide).[6] However, recurrence/primary resistance/progression of disease is all but inevitable, and generally poor outcomes are observed with second- and subsequent- lines of (predominantly) alkylating chemotherapy.[7] Re-resection and re-irradiation are used in select cases, but these remain controversial.

Recently, genomic analysis of e-GBM cases has revealed that almost 50% of these harbor somatic v-Raf murine sarcoma viral oncogene homolog B (BRAF) V600E mutations.[8] BRAF V600E mutations are found in a similar proportion of malignant melanomas (where they have been most intensively studied), and the mutation activates the BRAF kinase to promote constitutive downstream MAP kinase signaling, leading to activation of cell proliferation, and survival pathways. Activating BRAF V600 mutations are also found in multiple other cancer types, including lung adenocarcinoma (2%-4% of cases) and colorectal cancer (~10% of cases). They are also found in the e-GBM histological mimic, anaplastic pleomorphic xanthoastrocytoma (PXA; ~40%-60% of cases).[8] Genomic biomarker-directed targeted therapy with combinations of dabrafenib or vemurafenib (BRAF inhibitors) with (respectively) trametinib or cobimetinib (MEK1/2 inhibitors), is now standard in the management of patients with BRAF V600 mutant malignant melanoma[9,10]. Dabrafenib and trametinib have also shown significant activity in BRAF V600 mutant non-small cell lung cancer[11]. However, results with dabrafenib and trametinib were less impressive in BRAF V600 mutant colorectal cancer, where primary resistance is mediated through EGFR ligation, suggesting cancer-type specificity in therapeutic actionability.[12] There is limited, but increasing, published evidence on dabrafenib and trametinib in BRAF V600 mutant primary adult gliomas. Overall, current data suggest that BRAF V600E could be therapeutically actionable in GBM. A basket trial of vemurafenib monotherapy included (at least) 4 patients with BRAF mutant GBM, 3 of whom achieved stable disease as their best response, and one with primary progression.[13] An abstract reporting preliminary results from NCT02034110 basket trial

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of dabrafenib and trametinib reported, for 37 high-grade glioma patients, an overall response rate of 27%.[14] It is unclear how many, if any e-GBM patients have been recruited to this study.

Here we describe a case of a young adult patient with primary treatment-resistant BRAF V600E mutant e-GBM who achieved prolonged tumor shrinkage after commencing oral dabrafenib and trametinib. This case provides additional clinical evidence supporting the therapeutic actionability of BRAF V600E mutations, in the e-GBM variant of GBM, with combined BRAF and MEK1/2 inhibition, offering another potential treatment strategy for these patients with limited treatment options and otherwise poor prognoses.

## Clinical case

A 19-year-old woman with a 6-month history of intermittent headaches and visual disturbance presented to the Emergency Department with acute onset, severe headache, followed by a rapidly deteriorating level of consciousness. A computed tomography (CT) scan of the head was performed on admission, revealing a left temporal intracerebral hematoma measuring $\sim 47 \times 35$mm (Fig. 1a, upper left panel) with intraventricular and subarachnoid extension (Fig. 1a, upper right panel). A subsequent CT angiogram failed to detect any underlying vascular abnormality. On the same day, the patient underwent a decompressive craniectomy and partial evacuation of the contents of the hematoma. Subsequent magnetic resonance imaging (MRI) revealed a thick area of contrast enhancement in the medial aspect of the left temporal lobe, suspicious for an underlying tumor (Fig. 1, lower panels). A biopsy was performed and an initial histological diagnosis of a pleomorphic xanthoastrocytoma (PXA) was made.

The patient was later admitted electively for a 5-aminolevulinic acid- (5-ALA-) guided resection of the tumor. Complete macroscopic resection was achieved, supported by the absence of visible residual fluorescence intraoperatively, and the absence of enhancement on the postoperative MRI scan (Fig. 1b). Further histological assessment of the tumor showed a lack of pericellular reticulin, with no convincing xanthomatous cells or eosinophilic granular bodies to support the original diagnosis of PXA. The tumor was instead composed of pleomorphic epithelioid (GFAP-positive) glial cells and showed positive immunohistochemistry for cytoplasmic BRAF V600E protein (Fig. 1b). Next generation sequencing of somatic tumor cell DNA confirmed a BRAF V600E mutation and the absence of mutations in the IDH1 or IDH2 genes. The tumor cells were TERT-negative and H3F3A-negative by immunohistochemistry, with a MIB fraction of $>$20%, with an unmethylated MGMT promoter. Taken together, the integrated diagnosis (using the WHO 2016 classification) was revised to a high-grade BRAF mutant epithelioid glioblastoma (e-GBM).

After recovery from surgery, radiotherapy (60 Gy in 30 fractions) was administered, concomitantly with temozolomide chemotherapy (75 mg/m$^2$ daily). However, a post-radiotherapy MRI scan (Fig. 2a) revealed a new $26 \times 13$ mm enhancing nodule in the resection cavity of the medial left temporal lobe associated with new (smaller) inferiorly located nodules, all of which were likely to signify tumor growth rather than pseudo-progression.

Dabrafenib (300 mg daily) and trametinib (2 mg daily) were then commenced in combination in 28-day cycles as the sole ongoing treatments, accessed through a compassionate access program. The tumor was responsive to combination therapy, with MRI evidence of tumor volume reduction in the medial left temporal lobe after 2 months of treatment (Fig. 2b). This improvement persisted through 6 cycles of the dabrafenib and trametinib therapy (Fig. 2c). At the end of the 6th cycle, the patient developed a drug-related rash and liver function derangement, and the treatment regime was interrupted for 2 weeks. A decision was then taken to continue the dabrafenib and trametinib combination therapy for a further 3 months. Following this period, the patient developed a second and significant episode of drug-related rash and hepatitis, with an associated neutropenia. At this point, the patient had been on dabrafenib and trametinib for 11 months and a joint decision was made to interrupt the treatment regime given significant toxicity and effects on quality of life, and the likelihood of encountering similar (class effect-related) issues with alternative compassionate access BRAF- $\pm$ MEK1/2- targeted therapy.

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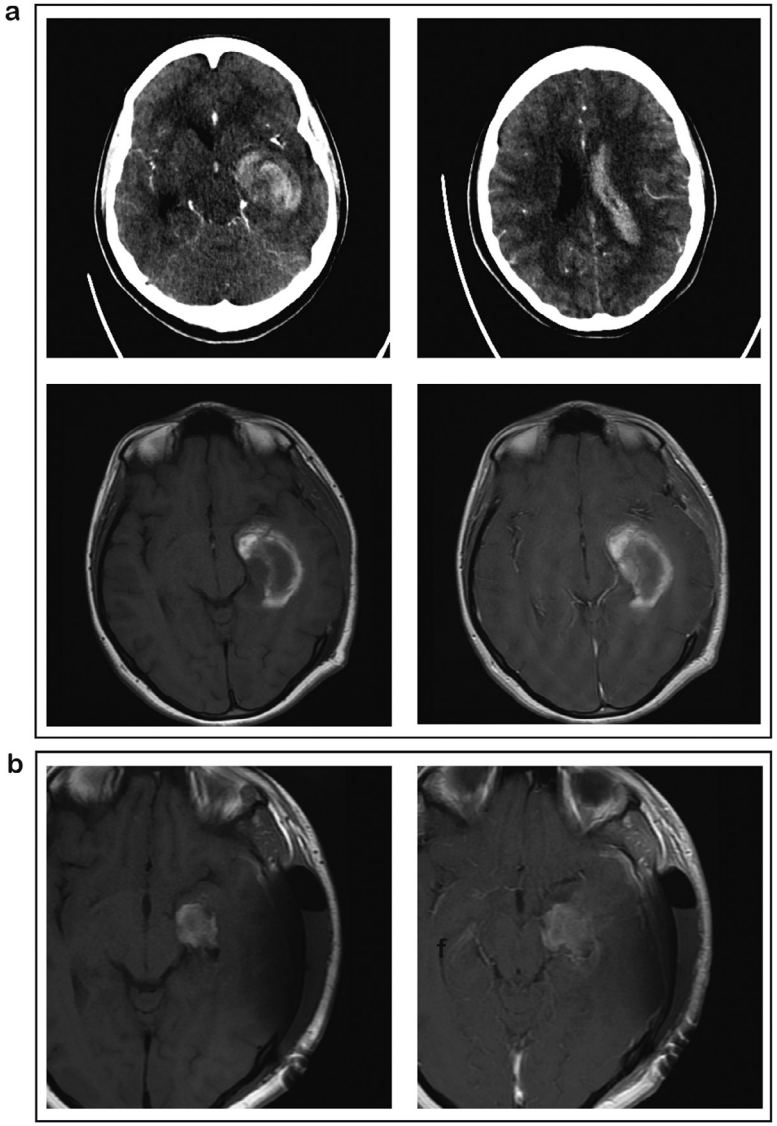


**Fig. 1.** Radiological features upon presentation and postoperatively, with histological features.
**(a) Upper left panel:** CT head showing a $49 \times 33 \times 28$ mm heterogeneous hematoma in the left temporal lobe, involving the left temporal horn. **Upper right panel:** CT head showing intraventricular extension of hemorrhage into the left lateral ventricle. **Lower left panel:** Pre-contrast MRI Head (T1-weighted) showing a large area of heterogeneous mixed signal intensity in the anterior and medial part of the left temporal lobe in keeping with a hematoma containing blood degradation products at different stages of evolution**. Lower right panel:** Post-contrast MRI Head (T1-weighted) showing a relatively thick area of contrast enhancement in the medial part of the left temporal lobe (arrow) suggestive of a glioma.
**(b)** MRI images of head pre- (**left panel**) and post- (**right panel**) contrast following resection of the left medial temporal lobe tumor. T1 hyperintense blood products seen in the medial aspect of the resection cavity with no enhancement to suggest residual tumor.
**(c)** Histological appearances of a representative haematoxylin and eosin-stained section (left panel) demonstrating a high-grade glioma with epithelioid/giant cell cytomorphology and a high degree of nuclear atypia/pleomorphism, with positive immunohistochemical for BRAF V600E within tumor cell cytoplasm using a BRAF V600E-specific antibody (**right panel**). Scale bar = 40 μm. (Color version of figure is available online.)

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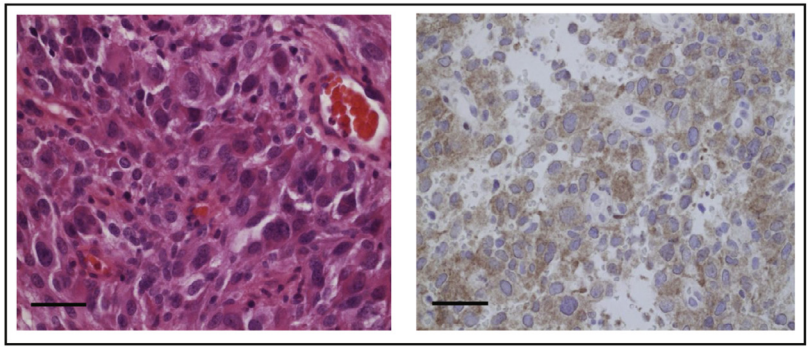


**Fig. 1.** Continued

Two months following the interruption of dabrafenib and trametinib therapy, the patient was readmitted due to a severe headache, similar in nature to the headache experienced at initial presentation. An MRI scan was performed which revealed a new enhancing nodule at the site of the previous resection, in keeping with primary tumor growth (Fig. 2d). The rash and liver function derangement had resolved, and it was decided to restart the dabrafenib and trametinib at the same doses: initially 4 weeks of dabrafenib monotherapy, followed by reintroduction of trametinib as combination therapy. The frequency of trametinib was then reduced to alternate day administration due to constitutional symptoms. Subsequent imaging carried out every 3 months following the recommencement of dabrafenib and trametinib demonstrated a sustained partial response, with no evidence of new abnormal parenchymal or meningeal enhancement or tumor progression for 18 months. A year after recommencement, the patient developed arthralgias, and the trametinib was subsequently stopped (cycle 27); cycle 28 onwards consisted of dabrafenib monotherapy at the same dose, which was then well tolerated.

Two months later the patient presented with acute onset lower back pain radiating into the legs. An MRI scan of the whole spine was performed, revealing an intermediate T2 signal, low T1 signal, tumor which displayed homogeneous contrast enhancement. This intradural extramedullary tumor measured $\sim 15 \times 13 \times 31$ mm, was located in the spinal canal at the level of T12/L1 (Fig. 3a) and resulted in cord compression (Fig. 3b). In addition, MRI imaging of the head revealed extensive nodular leptomeningeal tumor dissemination (Fig. 3c+d). This definitive on-treatment disease progression occurred 19 months following the recommencement of dabrafenib and trametinib therapy, corresponding to a total of 29 months from the initiation of dabrafenib and trametinib.

Palliative radiotherapy for the spinal drop metastasis causing spinal cord compression was given with the aim of preserving mobility. A follow-up MRI scan confirmed further spinal and primary disease progression, and the patient commenced on PCV combination chemotherapy: Procarbazine (100 mg/m$^2$ daily for 10 days, orally), lomustine (100 mg/m$^2$ as a single dose on day 1, orally) and vincristine (1.5mg/m$^2$ as a single dose on day 1, intravenously), in 6-weekly cycles. The patient's disease continued to radiologically progress after just 2 cycles of PCV. Active anti-cancer treatment was stopped, and the focus of care was changed to symptomatic management in concert with the palliative care team. The patient died 42 months and 21 days after their initial presentation, 39 months and 21 days after starting primary radiotherapy, and 37 months and 13 days after initially starting dabrafenib and trametinib.

## Discussion

Despite being the most common primary CNS malignancy in adults, the prognosis of GBM patients remains dismal (with median overall survival of around 18 months despite optimal

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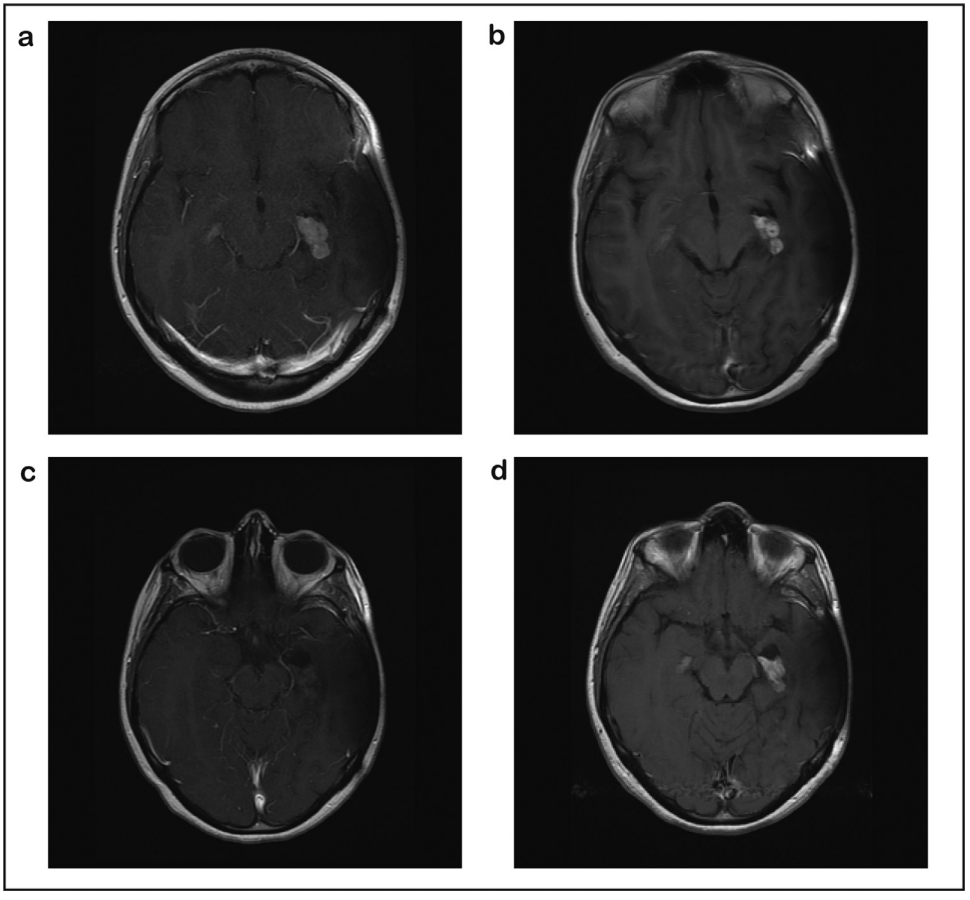


**Fig. 2.** Imaging showing radiological response to dabrafenib and trametinib and subsequent tumour progression following interruption of BRAF and MEK1/2 inhibition.
**(a)** Post-radiotherapy axial post-contrast T1-weighted MRI image showing a new $26 \times 13$ mm enhancing nodule in the resection cavity in the medial left temporal lobe.
**(b)** Axial post-contrast T1-weighted MRI image after 2 months of dabrafenib and trametinib treatment, showing a reduction in nodular enhancement consistent with an anti-tumor response.
**(c)** Axial post-contrast T1-weighted MRI image after 5 months of dabrafenib and trametinib treatment, showing a further reduction in nodular enhancement consistent with an ongoing anti-tumor response.
**(d)** Axial post-contrast T1-weighted MRI image following interruption of the dabrafenib and trametinib, demonstrating recurrence of nodular enhancement in the left medial temporal lobe.

treatment) and is associated with a poor quality of life. A newly defined, rare variant of IDH wild-type glioblastoma introduced in the WHO 2016 CNS tumor classification is e-GBM, and is an aggressive disease that affects comparatively younger populations than other GBM variants.[2] The diagnosis of e-GBM relies on a combination of radiological, histological and genomic features. Mass effect, seen as a result of vasogenic oedema and necrotic cystic areas, features prominently on radiology[15]. Histologically, these tumors are comprised of eosinophilic clusters of epithelioid (melanocyte-like) cells with eccentric nuclei and distinctive nucleoli.[16] As evidenced in the case presented here, and in other case series, histopathological distinction between e-GBM and PXA can prove challenging.[17] Moreover, other studies have concluded significant molecular overlap between these distinct entities, highlighting a possible close relationship between them.[16]

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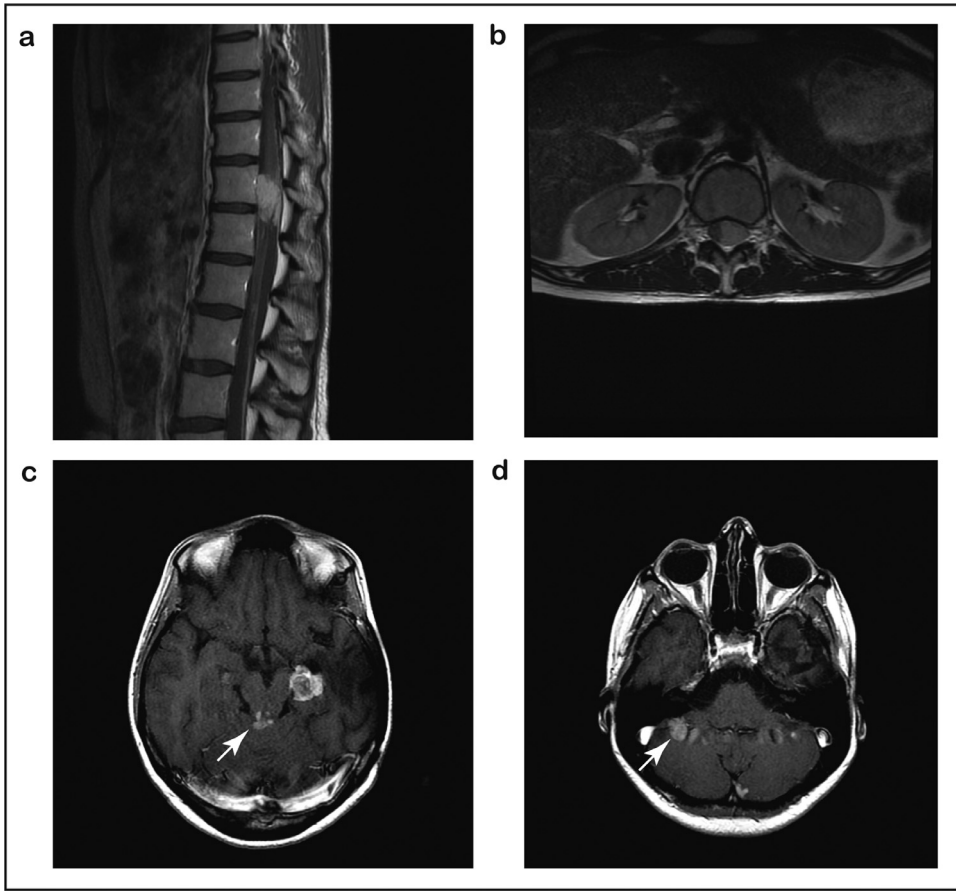


**Fig. 3.** Radiological evidence of leptomeningeal and parenchymal progression.
**(a)** Post-contrast, sagittal T1 MRI image showing a ~15 × 13 × 31 mm intradural extramedullary tumor in the spinal canal at the level of T12 and L1.
**(b)** Axial T2 MRI spine image showing displacement of the spinal cord to the right with evidence of spinal cord compression.
**(c and d)** Axial T1 MRI imaging demonstrating leptomeningeal dissemination of the progressing tumor (arrows). A new (~20 × 20 mm) enhancing nodule was found in the left medial temporal lobe (c) and new enhancing nodules were found in the posterior fossa: Quadrigeminal cistern (~11 mm), (d) overlying the left medial cerebellum (~11 mm) and the inferior right cerebellar hemisphere (~5 mm).

Dysregulation of the pro-proliferative and pro-survival MAPK cascade is well established as a driving feature of many peripheral and CNS tumors.[18] Notably, replacement of a valine with glutamic acid in the 600th codon of BRAF protein (BRAF V600E) is a common finding in PXAs, melanomas, e-GBMs, and other tumor types including other high grade gliomas.[19] This activating mutation leads to constitutive activity of BRAF, leading to MEK1/2 activation.[20]

The advent of novel orally bioavailable small-molecule BRAF inhibitors, including vemurafenib and dabrafenib, has revolutionized the management of BRAF V600 mutant melanomas.[21,22] Since dabrafenib may have greater CNS penetration than vemurafenib, it may be a superior molecule for targeting BRAF V600 mutant brain tumors.[23] Furthermore, drug resistance to therapy can be delayed with supplementation with a MEK1/2 inhibitor (eg, trametinib), which has been shown to improve survival rates in melanoma patients.[24] The report that a patient with GBM who developed acquired resistance to another BRAF inhibitor (vemurafenib,

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given in combination with cobicistat) achieved a complete radiological response with dabrafenib and trametinib[25] suggests that MEK1/2 may be important in resistance to BRAF inhibition, and that combined inhibition of BRAF and MEK1/2 may be a superior therapeutic strategy to BRAF inhibition alone, analagous to the therapeutic paradigm in melanoma.

In the case presented, the patient's disease progressed through primary chemoradiation. The efficacy of concomitant chemoradiation, the standard primary treatment for GBM regardless of subtype, is not definitively known for e-GBM. Importantly, our case describes a significant and prolonged response to BRAF and MEK1/2 inhibition (and later to BRAF inhibition alone). This demonstrates that at least a subset of BRAF V600E mutations are therapeutically actionable in e-GBM and opens up another possible treatment strategy for this poor prognosis group of patients, and may spare patients (or delay) the significant toxicities of chemotherapy (which would be the standard alternative treatment, but which is of uncertain efficacy). Our findings are consistent with the reported efficacy of dabrafenib and trametinib in combination in a basket trial (presented in abstract form; NCT02034110[14]). In this trial, the interim ORR for high grade glioma patients was 27% (n = 37), with 6 patients achieving a complete response (with a 12 month duration of response of 80%). The 12 month PFS and OS for the high grade glioma patients were 34% and 61%, respectively. Younger patients (<40 years old) achieved a higher response rate. We await eagerly the publication of the detailed results from this trial.

A recent study reported 2 cases of BRAF V600E eGBM treated with combinations of targeted therapy with only modest, short-lived responses.[26] Both cases were in young adults who had leptomeningeal spread at diagnosis. The first patient was treated with primary dabrafenib (150 mg, twice daily) and trametinib (at a high dose of 4 mg, daily) concomitantly with a 3 Gy fraction of radiotherapy to attempt to improve intracranial penetration. After a good initial clinical and radiological response, parenchymal and leptomeningeal progression was noted just 3 months after commencement of targeted therapy. The second patient was treated with primary vemurafenib, later having cobimetinib added in combination, with a good clinical and radiological response after 4 weeks. At this point the targeted therapy was stopped and concurrent chemoradiation with temozolomide commenced, with disease progression one week into radiation treatment. Vemurafenib and palbociclib (a CDK4/6 inhibitor) was commenced, resulting in a good clinical response, stable disease (using CT) on the first imaging on treatment, but a PFS not exceeding 8 weeks.

While a recently reported paediatric case of e-GBM showed a radiologically complete response after 4 months of vemurafenib treatment,[27] a basket study of vemurafenib monotherapy has also reported outcomes,[13] although it is unclear which (if any) patients in these trials had *epithelioid* GBM, and only 4 patients had a definitive diagnosis of any type of GBM. In these patients with GBM, no objective responses were observed (3 patients having stable disease and one patient having primary progression), and PFS outcomes for these patients were 12.9, 3.7, 3.6 (censored) and 1.8 months, suggesting that vemurafenib alone may have limited efficacy in this patient population. At least 6 further cases have been treated with anti-BRAF monotherapy, with overall survivals ranging from less than 2 months to over 100 months.[27-32] Overall, the general efficacy of combination therapy with BRAF-± MEK1/2 inhibitors in V600E positive e-GBM remains unclear, and clinicians should continue to report cases and case series treated with targeted therapy (both successfully and unsuccessfully).

Although reports are limited in number, e-GBM appears to have a predilection for leptomeningeal spread, which may partly explain the poor prognosis associated with this disease. Consistently with primary and secondary brain tumors, leptomeningeal disease is a very poor prognostic sign. The poor response rates of leptomeningeal disease to cytotoxic chemotherapy and targeted treatments suggest either poor drug penetration into tumors or a change in the biology of the disease. The excellent intracranial penetration of dabrafenib makes the latter seem more likely; possibly the increased 2-dimensional (leptomeningeal) vs 3-dimensional (parenchymal) growth, or the relative activation of specific signaling pathways in distinct tumour microenvironments, results in reduced tumoral dependence on BRAF signaling. Even in melanoma where this is better studied, outcomes are poor with BRAF V600 mutant leptomeningeal spread.

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Taken together, the case presented here adds weight to the therapeutic actionability of BRAF V600E mutations in e-GBM with BRAF ± MEK1/2 inhibitors, suggesting a further treatment option for patients with this poor prognosis disease. Our findings suggest that a primary objective of e-GBM treatment should be to delay leptomeningeal spread as long as possible and to ensure that patients are offered targeted treatment while it is likely to be effective. We therefore suggest that management of patients with BRAF V600E mutant e-GBM should involve early and sustained BRAF ± MEK1/2 inhibition with dabrafenib ±± trametinib. However, the optimal treatment paradigm of patients with BRAF V600 mutant GBM (including eGBM) remains unclear and its definitive delineation requires a first line trial of standard treatment (radiation ± temozolomide) vs BRAF- and MEK1/2- targeted therapy in combination (dabrafenib and trametinib). In the meantime, treatment decisions must be carefully individualized. Given the propensity for early leptomeningeal spread in patients with BRAF V600 mutant eGBM, we recommend baseline staging of both the brain and spine in these patients, as well as *consideration* of first line BRAF- and MEK1/2- targeted therapy, particularly for those patients where gross total resection has not been achieved, those with large volume disease pre- or post-operatively, and imaging features that increase risk for leptomeningeal spread. For eGBM patients who are not receiving targeted therapies, we recommend more frequent MRI staging scans of the spine and brain to detect tumour progression as early as possible, where introduction of targeted therapy is likely to be more effective.

## Author contributions

RK and GJD conceptualised the manuscript. AV and AJ summarized the case study and drafted the manuscript. TS, RJ, SJJ, FPH and GJD made decisions about patient treatment, provided direction for key discussion points and critically reviewed and edited the manuscript. TD provided radiological imaging and interpretation and critically reviewed the manuscript. KA provided histological images as well as descriptions of pathology. TS provided information regarding neurosurgical management. GJD finalised the figures and manuscript. All authors read and approved the final manuscript and gave their consent for publication.

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## Patient confidentiality

The patient whose case is reviewed here generously provided their permission to publish their case in this manner, and we thank them and their family. No patient-identifiable information is included in this manuscript.

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