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*Case Report*

# Treatment of *BRAF* V600E mutated ganglioglioma of the third ventricle with dabrafenib

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## ABSTRACT

**Background:** Ganglioglioma (GG) of the third ventricle is rare. Surgical excision of tumors in this location is associated with high morbidity due to nearby eloquent brain centers. Alternative treatments, when available, should be considered to reduce risks of surgical treatment.

**Case Description:** We present the case of a 21-year-old female diagnosed with a BRAF V600E mutated GG of the third ventricle. After an endoscopic biopsy and insertion of a ventriculoperitoneal shunt, the patient was started on the *BRAF* inhibitor dabrafenib, as an alternative to surgery or radiation. Nearly 2 years after starting dabrafenib, her tumor appearance on serial magnetic resonance imaging is stable, and she has maintained a good quality of life with no new neurological symptoms.

**Conclusion:** The disease control thus far suggests targeted medical therapy of GG of the third ventricle with *BRAF* inhibitors may have efficacy and should be a considered treatment modality.

**Keywords:** *BRAF* inhibitor, Dabrafenib, Ganglioglioma, Targeted therapy, Third ventricle

## INTRODUCTION

Gangliogliomas (GGs) are rare, well-differentiated tumors comprising dysplastic cells of neuronal and glial origin, accounting for 1.3% of central nervous system (CNS) tumors in adults.[17] GGs may be found in any location of the CNS[17] and affect all age groups, but predilect children and young adults in the first three decades of life.[17] Most GGs develop in the supratentorial region with a temporal predominance (up to 85%).[17] GGs are classified as WHO grade I and do not recur following complete surgical excision, the mainstay treatment for surgically accessible GGs.[11] The 7.5-year recurrence-free survival rate for GG following surgical resection is 97%.[11] Tumor recurrence, as well as malignant transformation of the glial component (rarely of the neuronal one) with anaplastic progression, may occur (WHO grade II and III).[11]

Ten to sixty percent of GGs, depending on anatomic location have an activating p.V600E mutation in the *BRAF* oncogene.[13] Most *BRAF* mutations are missense mutations at codon 600 which results in glutamic acid instead of valine acid.[3,14] This mutation is associated with a shorter recurrence-free survival,[2] and a higher regrowth rate in brainstem GG compared with wild-type.[1] *BRAF* p.V600E mutations are also present in other neuroepithelial tumors such

as pilocytic astrocytoma, pediatric IDH-wildtype diffuse astrocytoma, epithelioid glioblastoma, and polymorphous low-grade neuroepithelial tumor of the young.[6,9,10,13,15] Genetic mutations in GGs cause activation of the MAP kinase signaling pathway (also known as the RAF-MEK-ERK pathway), which is critical for cancer cell survival, proliferation, and treatment resistance.[4] Given the high rate of *BRAF* p.V600E mutation, patients with recurrent GGs following surgical excision and chemotherapy have been treated with mutation-specific kinase inhibitors.[5]

We present the case of a young patient with a third ventricle GG treated with the *BRAF* inhibitor dabrafenib.

## CASE DESCRIPTION

### Presentation

A 21-year-old female presented to the emergency department in November 2017 with a 2-month history of a worsening headache in the frontal and occipital regions. This was associated with photophobia and nausea, blurred vision, neck stiffness, and vomiting. She had no significant background medical history. The neurological examination was clinically unremarkable.

### Imaging

Computed tomography imaging demonstrated hydrocephalus with severe lateral ventriculomegaly with a deviation of the septum pellucidum to the left, effacement of the sulcal spaces, basal cisterns, and tonsillar herniation. Subsequent magnetic resonance imaging (MRI) demonstrated a lobulated mass within the third ventricle which demonstrated mildly increased signal on $T_2$ weighted imaging [Figure 1a], isodensity on $T_1$ weighted imaging [Figure 1b], and no restricted diffusion [Figure 1c]. It showed enhancement after gadolinium. There was absent cerebral spinal fluid (CSF) flow through the cerebral aqueduct and no dilation of the fourth ventricle.

### Surgical treatment

The patient underwent endoscopic exploration with biopsy of the mass protruding through the foramen of Monroe followed by septum pellucidotomy and ventriculoperitoneal shunt insertion (Codman Certas plus programmable valve set at 5).

Following the operation and given the anatomic location and tumor grade, conservative management with serial MRIs was initially undertaken in consideration of the potential morbidity of a surgical approach to the third ventricle. An MRI in February 2018, and in July 2018, demonstrated a stable appearance of the GG and reduced ventricular size. The patient remained neurologically well with resolution of her headaches and maintained her normal daily functioning. Follow-up MRI in March 2019 showed subtle tumor growth. There was increased mass effect on the midbrain and tectal plate due to the increased size of the dorsal cystic component of the tumor (from 11 × 4 × 8 mm to 24 × 12 × 14 mm) [Figure 1d]. This increase in tumor size and recurrence of headaches led to a multidisciplinary discussion. The potential surgical morbidity associated with an approach to the third ventricle, and the significant risk of toxicity from radiation in view of her anticipated long survival, led to consideration of medical treatment.

### Medical treatment

In consideration of the tumor growth and the presence of a *BRAF* p.V600E mutation, we suggested the use of the *BRAF* inhibitor dabrafenib. After discussion with the patient, a final decision was made to proceed with medical treatment. The patient commenced dabrafenib at 150 mg twice daily in July 2019. MRI 4 months later in October 2019 demonstrated a significant reduction in tumor size from 22 × 12 mm to 17 × 8 mm [Figure 1e]. One month later she developed painful feet secondary to pitted keratolysis, likely secondary to dabrafenib. In December 2019 her dose of dabrafenib was reduced to 75 mg twice daily. Three MRI scans performed in August 2020, February, March, and June of 2021 all demonstrated a stable tumor appearance [Figure 1f]. The patient stated her headache symptoms were stable, which she still experienced occasionally. Her painful feet subsided within 4 weeks.

### Histology

Histology was consistent with a WHO grade I GG [Figure 2a and b]. The hematoxylin and eosin-stained tissue sample display the presence of dysplastic ganglion cells characterized by large neurons with abnormal localization, and loss of cytoarchitectural organization. There is also a neoplastic glial component with no necrosis seen [Figure 2a and b]. Mass Array Analysis demonstrated a *BRAF* V600E c.1799T>A activating mutation.

## DISCUSSION

This case presented shows the multidisciplinary management of a third ventricle GG. Although surgery was initially considered, the patient's young age and the potential high post-operative morbidity led the multidisciplinary team to consider targeted therapy with the *BRAF* inhibitor dabrafenib.

Patients with third ventricle GGs may present with symptoms of raised intracranial pressure secondary to obstruction of CSF circulation. Their treatment includes surgical resection

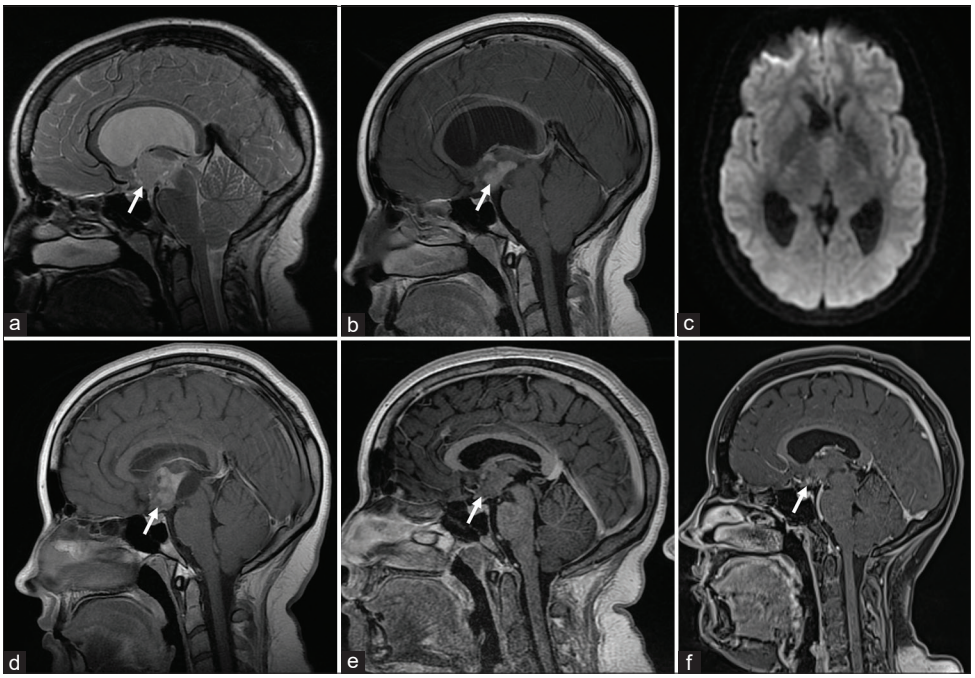


**Figure 1:** Serial magnetic resonance imaging (MRI) images of the ganglioglioma. Sagittal $T_2$ weighted MRI (a), Sagittal $T_1$ weighted MRI (b), diffusion-weighted imaging (c), Sagittal $T_1$ weighted MRI (d), Sagittal $T_1$ weighted MRI from October 2019 showing a reduction in tumor size (e), and a Sagittal $T_1$ weighted MRI from March 2021 showing a stable tumor appearance (f).

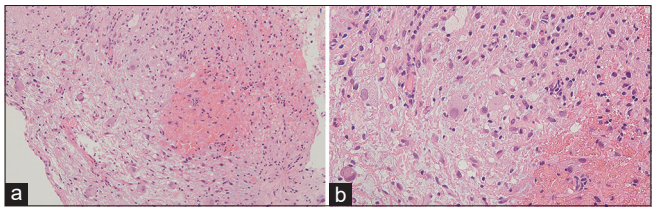


**Figure 2:** Hematoxylin and eosin image of ganglioglioma from the illustrative case in low (a) and high power (b) magnification.

and drainage of CSF to decrease intracerebral pressure. As the third ventricle is located centrally in the brain, GGs here present a surgical challenge, with a limited potential for complete resection due to nearby eloquent brain structures.

In avoiding the potential complications from surgery, our patient had a good treatment response to dabrafenib. However, she experienced some mild complications that prompted a dosage reduction. This finding is supported by case reports in the literature for the BRAF inhibitors dabrafenib and vemurafenib. Higa *et al*. reported a case of a third ventricle GG and reviewed the available literature.[8] In total, they found six cases of third ventricular GG reported. The surgical approach and the extent of resection in these lesions was variable. In the case reported by Higa *et al*. there was no *BRAF* mutation detected. Further, Miyake *et al*. report a *BRAF* V600E mutated hemorrhagic GG of the third ventricle that underwent endoscopic subtotal tumor resection.[12]

We did not find a report of a third ventricle GG treated with *BRAF* inhibitors. Although surgically accessible, we felt that a surgical approach was associated with a high risk of complications. The literature evidence for the management of other GGs prompted us to consider the use of *BRAF* inhibitors in the presented case. Conservative management was attempted initially, but tumor growth prompted us to begin medical treatment. A good response with tumor control was observed with the sole use of dabrafenib at 2 years. Mild side effects were successfully controlled with a reduction in the dosage of dabrafenib.

*BRAF* mutated GGs have been treated successfully with *BRAF* inhibitors, in multiple anatomic locations.[7] Garnier *et al*. reviewed 14 patients with GG treated with BRAF inhibitors. Among these patients were some who took a *BRAF* inhibitor alone, and some who took concomitant chemotherapeutics, such as the *vinca* alkaloid vinblastine. These include an adult with *BRAF* V600E mutated spinal GG treated with vemurafenib. He had a partial response within 2 months, which was sustained for over a year. The patient stopped treatment due to side effects, and the tumor did not show progression for 21 months after treatment discontinuation.[7] Further, a 21-year-old male with temporal lobe and posterior brainstem GG had gross total resection and vincristine, carboplatin, radiotherapy, temozolomide, irinotecan, and bevacizumab before starting *BRAF* inhibitor treatment. He experienced GG recurrence 11 years later and began dabrafenib and gemfibrozil. He experienced no side

effects and had a partial response at 2 months and had GG recurrence after stopping the *BRAF* inhibitor.[16]

This raises an important question: what is the appropriate treatment duration for *BRAF* inhibitors in treating GGs to achieve a sustained response? Further studies are required but *BRAF* inhibitors should be considered within the armamentarium of the treating physician.

## CONCLUSION

This case demonstrates the efficacy of *BRAF* inhibitors against GGs in the third ventricle and highlights the need for further investigation of this treatment modality. It also highlights the importance of a multidisciplinary approach towards complex lesions like these. Targeted medical treatment for GGs of the third ventricle, which avoids high morbidity surgery and maximizes their quality of life, is a promising treatment method for third ventricle GGs.

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### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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