Article published online: 2024-08-29

Clinical Outcome of Patients with Epithelioid Glioblastoma Harboring BRAFV600E Mutation; A Single Institution Experience

Preethi Subramanian[1] Anindita Das[1] Srinivas Chilukuri[1] Adhithyan Rajendran[1] Sushma Patil[1] Sujith Kumar Mullapally[1] Uday Krishna[1] Roopesh Kumar[2] Rakesh Jalali[1]

[1] Neuro-Oncology Cancer Management Team, Apollo Proton Cancer Centre, Chennai, Tamil Nadu, India
[2] Institute of Neurosurgery, MGM Healthcare, Chennai, Tamil Nadu, India

Address for correspondence Rakesh Jalali, MD (Radiation Oncology), Apollo Proton Cancer Centre (APCC), Chennai, Tamil Nadu 600041, India (e-mail: rjalali@apollohospitals.com).

South Asian J Cancer

Abstract

Rakesh Jalali

Purpose Epithelioid glioblastoma (GBM) is a rare variant of GBM. The study aimed to look into clinicopathological details and outcomes of patients with epithelioid GBM harboring BRAFV600E mutation from a single institution.

Methods Ten cases of epithelioid GBM diagnosed over the past 5 years were reviewed. All patients underwent surgical resection followed by adjuvant treatment as per protocol after initial diagnosis. Of these, seven patients were planned to redo surgery, reradiation, BRAF with MEK inhibitors, and bevacizumab based on clinical condition, magnetic resonance imaging findings, and progression-free survival after their recurrence. Four recurrent patients had received dabrafenib and trametinib.

Results All tumor locations were supratentorial. The median follow-up was 2.3 years and the median time to recurrence was 19 months from the diagnosis (range 4–36 months). Four recurrent patients received BRAF + MEK inhibitors. One patient who started dabrafenib and trametinib experienced local progression after 33 months, followed by lung and bone metastasis. One patient died due to multiple subacute hemorrhages, who was a known case of congenital vascular malformations, and two patients remained disease-free after a year and 2 years.

Conclusion Epithelioid GBM is a very rare, but well-documented entity. Therefore, careful preoperative imaging and detailed evaluation of genetic studies including *BRAF* V600E mutation are necessary for accurate diagnosis and appropriate selection of treatment for epithelioid GBM. Dabrafenib plus trametinib showed clinically meaningful activity in patients with BRAF V600E mutation-positive recurrent high-grade glioma.

Keywords

- epithelioid glioblastoma
- BRAF V600E inhibitors

DOI https://doi.org/10.1055/s-0044-1789605 ISSN 2278-330X

How to cite this article: Subramanian P, Das A, Chilukuri S, et al. Clinical Outcome of Patients with Epithelioid Glioblastoma Harboring BRAFV600E Mutation; A Single Institution Experience. South Asian J Cancer 2024;00(00):00–00.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

An inclusion in the World Health Organization (WHO) CNS Tumors 2016 classification involves the introduction of a distinctive form of glioblastoma (GBM) recognized as epithelioid glioblastoma (eGBM).[1] eGBMs can be recognized by their large epithelioid cells, which have plenty of pinkish cytoplasm, grainy chromatin, noticeable nuclei (sometimes resembling melanoma cells), and occasionally occurring rhabdoid cells.[2,3] The average age of onset for this specific tumor subtype is notably lower in comparison to that of conventional GBM. In some instances, eGBMs have been observed to develop from preexisting pleomorphic xanthoastrocytomas (PXAs).[4,5] A specific genetic mutation, BRAF-V600E (where valine is replaced by glutamic acid at position 600 of the B-Raf protein, which is involved in serine/threonine-specific protein kinase activity),[6] has been identified in 50 to 100% of cases of eGBM.[7] eGBMs harboring the BRAF V600E mutation have demonstrated a promising response to BRAF and MEK inhibitors.[8–12] The utilization of BRAF and MEK inhibitors leads to meaningful clinical changes .

The primary objective of this study was to elucidate the clinicopathological features as well as the subsequent outcomes of a collection of 10 cases of eGBM that underwent treatment at the Apollo Proton Cancer Centre situated in Chennai, Tamil Nadu, India.

Materials and Methods

All cases diagnosed as eGBM over the past 5 years were retrieved from the database of the Department of Neuro-oncology, Apollo Proton Cancer Centre, Chennai, Tamil Nadu, India. Between 2018 and 2023, 10 patients with eGBM were referred for radiation therapy. Of these, five were recurrent eGBMs. Surgical resection was done for all patients and the histopathological confirmation of the diagnosis was obtained. Immunohistochemistry (IHC) was conducted for all patients to analyze specific protein markers and BRAV600E mutation. The degree of surgical resection was assessed qualitatively either during the surgery itself by the surgeon or, if possible, by evaluating contrast-enhanced magnetic resonance imaging (MRI) images after the operation.

All patients received adjuvant radiation to a dose of 59.4 Gy/33 fractions or 60 Gy/30 fractions with concurrent temozolomide (75 mg/m^2) followed by adjuvant temozolomide as per protocol until recurrence. One patient was started with dabrafenib and trametinib instead of adjuvant temozolomide after initial radiation due to suspicion of progression. In recurrent settings, patients were considered to redo surgery, reradiation, BRAF with MEK inhibitors, and bevacizumab based on clinical condition, MRI findings, and progression-free survival. All cases were discussed in the Neuro-oncology Clinical Management Team at our institute.

Results

The median patient age at diagnosis was 34 years (range: 22–55 years). The male and female ratio was 1:1. All tumor locations were supratentorial. Among the cohort, a total of five patients were referred for adjuvant treatment after their initial surgical interventions. The other five patients exhibited indications suggesting the possible recurrence of eGBMs. The extent of surgical resection at the point of initial diagnosis consisted of gross total resection ($n = 7$, 70%), and subtotal resection ($n = 3$, 30%). All patients were positive for BRAFV600E on IHC.

The median follow-up was 2.3 years and the median time to recurrence was 19 months (range 4–36 months) from the diagnosis of eGBM (►**Tables 1** and **2**). An ependymal nodular lesion in ventricles and spine, lung, and bone metastatic lesions were seen in two patients (►**Fig. 1**). In recurrent situations, three patients underwent reexcision, four patients had

Table 1 Summary of the patients till last follow-up (not on BRAF + MEK inhibitors)

Patient	Age at diagnosis/ Sex	Recurrent Yes/No	Treatment regimens	Last FU status	Overall survival
1	23/M	No	On adjuvant temozolomide Regular follow-up	Regression	15 mo + NED
2	61/M	No	On adjuvant temozolomide, regular follow-up	Pseudoprogression	9 mo + NED
3	32/M	Ependymal spread with spine metastasis DFI-31 mo (►**Fig. 1A, B**)	Re-RT-craniospinal irradiation followed by boost (IMPT) to residual lesion followed bevacizumab	Leptomeningeal and brainstem involvement	44 mo + with progression-DOD
4	34/F	Local recurrence DFI-24 mo	Redo surgery + Re-RT (IMRT)	Dead due to disease progression	48 mo-DOD
5	34/M	Local recurrence DFI-14 mo	Defaulted FU after recurrence	Dead due to disease progression	17 mo-DOD
6	34/F	Local recurrence DFI-4 mo	Defaulted FU after recurrence	Dead due to disease progression	14 mo-DOD

Abbreviations: DFI, disease-free interval; DOD, dead of disease; F, female; FU, follow-up; IMPT, intensity-modulated pencil beam scanning proton therapy; IMRT, intensity-modulated radiation therapy; M, male; NED, no evidence of disease; Re-RT, reirradiation.

Table 2 Summary of the recurrent and response pattern till the last follow-up with BRAF + MEK inhibitors

Patient	Age at diagnosis/ Sex	Recurrent pattern (DFI)	Treatment regimens	Last follow-up status	Overall survival
1	36/F	Local recurrence (36 mo)	Redo excision followed by Re-RT-IMPT and BRAF + MEK inhibitors + bevacizumab	Stable (►Fig. 2A)	76 mo + NED
2	22/M	Local recurrent with hemorrhage (known case of congenital vascular malformations) (9 mo)	Redo excision followed by BRAF + MEK inhibitors	Dead due to multiple episodes of subacute hemorrhage	17 mo DOD
3	55/F	Local recurrence with hemorrhage (32 mo)	At pseudoprogression -bevacizumab followed BRAF + MEK inhibitors At local recurrence - Re-RT (IMRT) Distant metastasis – immunotherapy + BRAF + MEK inhibitors	Distant lung and bone metastasis on immunotherapy (►Fig. 1C, D)	38 mo + progression
4	34/F	Local recurrence (12 mo)	BRAF + MEK inhibitors + injection bevacizumab	Stable (►Fig. 2B)	26 mo + NED

Abbreviations: DFI, disease-free interval; DOD, dead of disease; F, female; IMPT, intensity-modulated pencil beam scanning proton therapy; IMRT, intensity-modulated radiation therapy; M, male; NED, no evidence of disease; Re-RT, reirradiation.

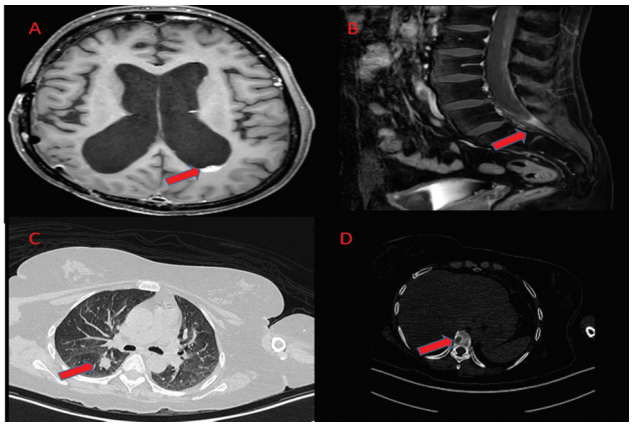

Fig. 1 (**A**) Ependymal nodule in ventricle. (**B**) Ependymal nodule in spine. (**C**) Distant lung metastasis. (**D**) Distant bone metastasis.

reradiation, and four patients received dabrafenib and trametinib. Two patients defaulted after recurrence and died due to disease progression. Bevacizumab was considered based on MRI findings and steroid dependency.

One patient who started dabrafenib and trametinib after adjuvant radiation experienced local progression after 33 months, followed by local recurrence with lung and bone metastasis (►Fig. 1C, D). One patient died due to multiple subacute hemorrhages, which was a known case of congenital vascular malformations, and two patients remained disease-free later (►Fig. 2A and B corresponds to 24 and 12 months of follow-up after BRAFV600E inhibitors, respectively).

Discussion

Due to the rarity of eGBM, there are limited published studies that focus on assessing outcomes specifically for individuals with this condition. This particular tumor tends to manifest in young adult group, as evidenced by a median age of 34 years observed in our case series. eGBMs are commonly found as tumors located in the diencephalon or, less frequently, as superficial masses within the cerebral hemispheres.[13] These tumors have apparent enhancement after contrast injection and show significantly restricted hyperintensive signals with mild perilesional edema (►Fig. 3). Hemorrhage and the dissemination of tumor cells into the leptomeninges are likely to be frequently observed during the time of diagnosis.[14–16]

The tumor exhibited characteristics of an astrocytic glioma, featuring high mitotic activity, microvascular proliferation, and necrosis. It primarily consisted of cohesive sheets of epithelioid or melanoma-like cells that displayed loose cohesion, ample cytoplasm, eccentric nuclei, and occasional presence of fibrillar or globular cytoplasmic inclusions, resembling rhabdoid cytology[7,17–20] (►Fig. 4). A minority of cases of extremely aggressive GBM also displayed limited areas that resembled the morphological characteristics of PXA.[21,22] Analysis of the genetic profile uncovered the presence of BRAF V600E mutations in a range of 50 to 93% within the subset of eGBMs.[23,24] Additionally, TERT promoter mutations were detected in 70% of cases, while homozygous deletions affecting CDKN2A/2B were observed in 79% of instances.[2,25] In our series, all patients were positive for BRAFV600E on IHC.

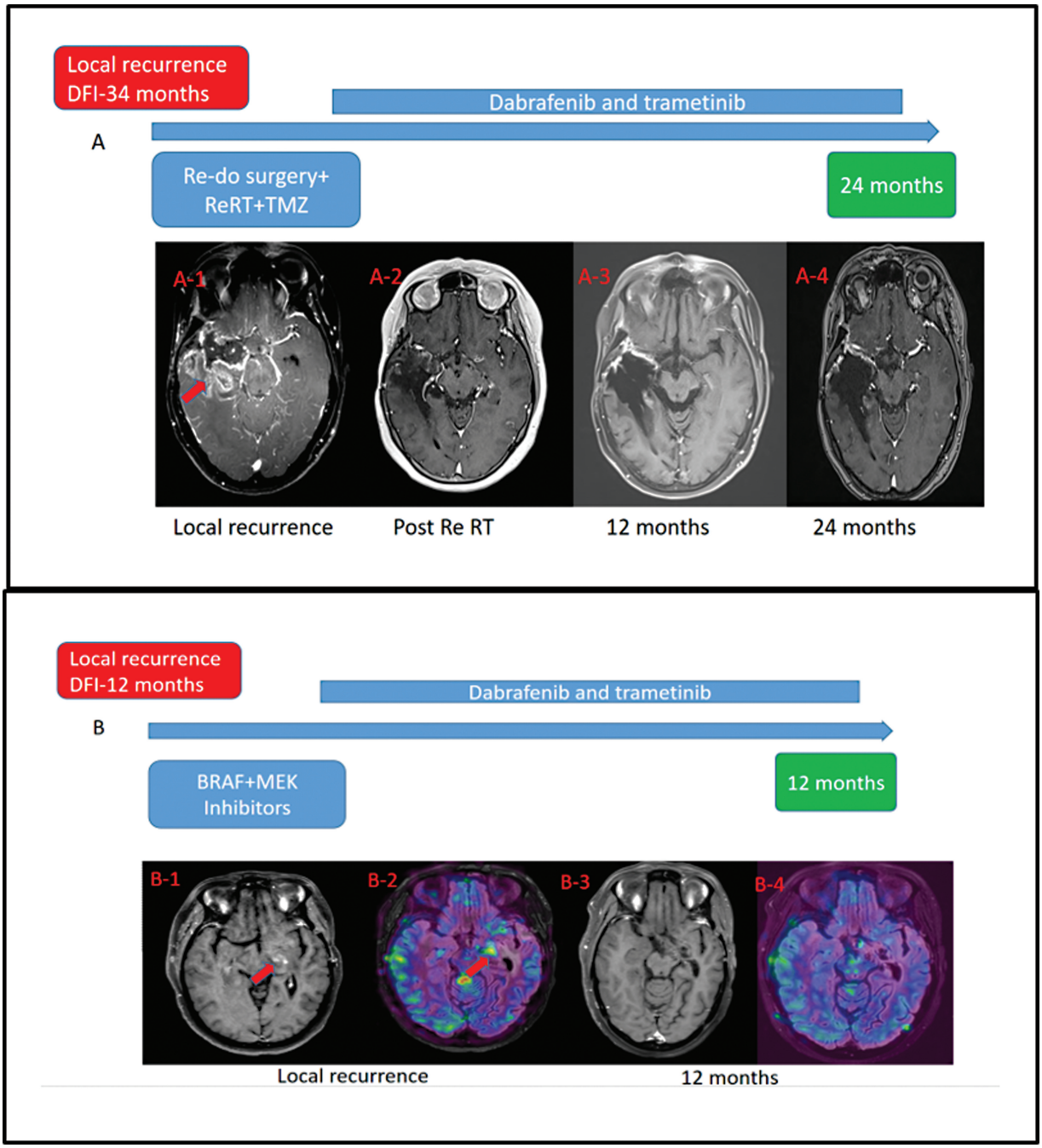

Fig. 2 Response of BRAF + MEK inhibitors. (**A**) Patient A; A1, local recurrence; A2, postsurgery and reradiation; A-3 and A4, no residual lesion on follow-up. (**B**) Patient B: B1 and B, local early recurrence; B3 and B4, regression of lesion during follow-up.

In contrast to the typical GBM, eGBM exhibits a distinct tendency to metastasize to extracranial organs and spread via cerebrospinal fluid dissemination. One patient had ependymal nodular spread in the ventricles and spine, while another patient developed distant lung with bone metastasis in this series (►**Fig. 1**). As a highly invasive brain tumor, the median survival time is only a few months (ranging from 6 to 31 months).[15,26] Our series showed the same (►**Tables 1** and **2**).

BRAF V600E mutation was detected in neuroepithelial tumors, including astrocytomas of WHO grade II and a gliosarcoma of WHO grade IV, as well as on GBMs with epithelioid histopathological features.[27,28] One of the extensively investigated focal points pertains to the proto-oncogene B-Raf (BRAF), which encodes a serine/threonine protein kinase situated within the RAS-RAF-MEK-ERK-MAP kinase pathway.[6] Within this context, the BRAF V600E mutation has garnered significant attention, manifesting itself in up to 7% of diverse human malignancies. This mutation triggers a substitution wherein valine is replaced by glutamine at position 600 within the amino acid sequence of the protein kinase. Directly addressing this genetic aberration, B-Raf kinase inhibitors such as vemurafenib or dabrafenib have emerged as notably efficacious therapeutic avenues. Particularly, these inhibitors have garnered approval for the treatment of advanced malignant melanomas that bear

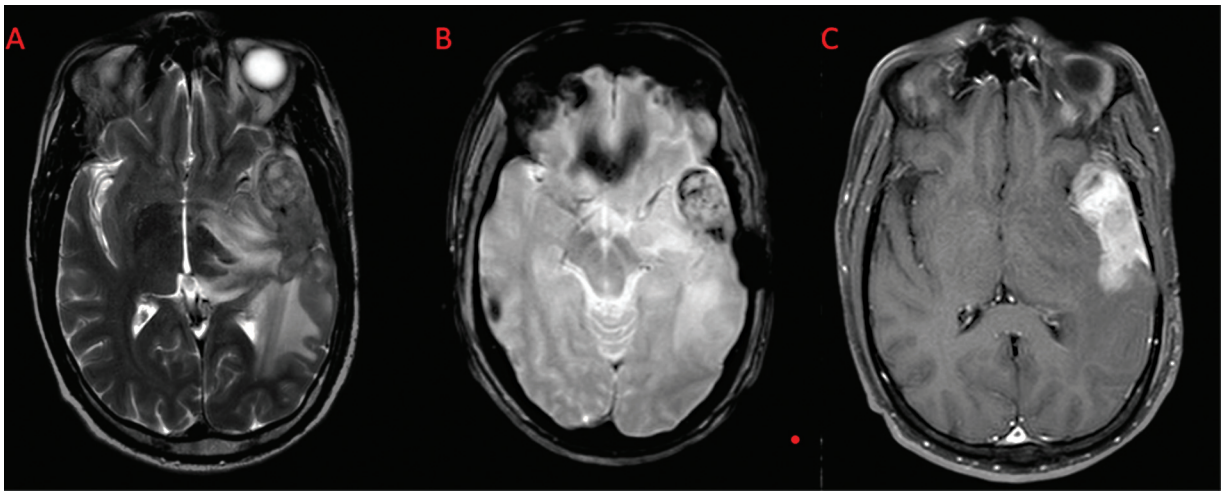

Fig. 3 The tumor in left temporal lobe showing hyperintensity on T2-weighted image (T2WI) with edema (**A**). Intratumoral hemorrhage on gradient echo (GRE) (**B**) and enhancement on T1W (**C**).

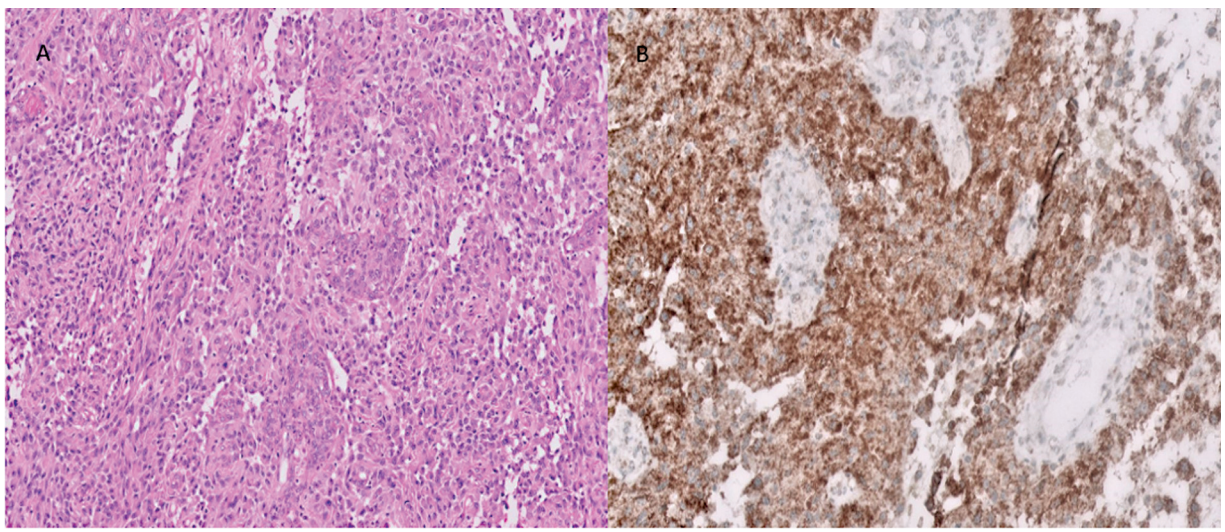

Fig. 4 (**A**) Hematoxylin and eosin (H&E) staining displayed abundant eosinophilic cytoplasm with rhabdoid features in the tumor cells. (**B**) BRAFV600E mutation on immunohistochemistry.

the BRAF V600E mutation.[29] Vemurafenib, an inhibitor targeting BRAF, has exhibited noteworthy clinical effectiveness among patients who harbor BRAF V600E-mutant melanoma brain metastases.[30] Moreover, its positive impact has extended beyond melanoma, demonstrating favorable outcomes in the context of various other malignancies.

Numerous case reports have documented promising outcomes in the context of targeted therapy for brain tumors characterized by the presence of the BRAF V600E mutation.[10,31,32] Examples of such tumors include ganglioglioma, PXA, and papillary craniopharyngioma.[29,33,34] Likewise, in mice carrying BRAFV600E gliomas, a combination therapy involving both BRAFV600E and MEK inhibitors resulted in diminished tumor growth when compared to the effects of solely inhibiting BRAFV600E.[35] The investigator-assessed objective response rate was 33% in high-grade glioma (32% in GBM) and 69% in low-grade glioma which is shown in an ongoing ROAR study.[36]

Within the scope of our investigation, a total of four patients received the BRAF inhibitor (dabrafenib) and the MEK inhibitor (trametinib). Our experiences are summarized in ►**Table 2**. The concurrent administration of dabrafenib and trametinib yielded a notable therapeutic response in a patient afflicted by eGBM multiforme harboring the BRAF V600E mutation. This treatment combination exhibited substantial efficacy while causing minimal adverse effects and preserving a favorable quality of life. Notably, three patients demonstrated sustained local control (►**Fig. 2**).

Conclusion

eGBM multiforme is a notably infrequent yet extensively documented entity. As a result, meticulous preoperative imaging, histomorphology, and molecular assessment are imperative to ensure precise diagnosis. Furthermore, multi-institutional prospective study is essential for additional

insights through the utilization of BRAF + MEK inhibitors, to gather a more comprehensive understanding of treatment outcomes over an extended period.

Conflict of Interest

None declared.

References

1 Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016;131(06):803–820
2 Nakajima N, Nobusawa S, Nakata S, et al. BRAF V600E, TERT promoter mutations and CDKN2A/B homozygous deletions are frequent in epithelioid glioblastomas: a histological and molecular analysis focusing on intratumoral heterogeneity. Brain Pathol 2018;28(05):663–673
3 Chatterjee D, Radotra BD, Aggarwal D, Madan R, Gupta SK. Analysis of 24 cases of epithelioid glioblastoma: experience from a tertiary centre of North India. Ann Diagn Pathol 2021;50:151679
4 Furuta T, Miyoshi H, Komaki S, et al. Clinicopathological and genetic association between epithelioid glioblastoma and pleomorphic xanthoastrocytoma. Neuropathology 2018;38(03):218–227
5 Alexandrescu S, Korshunov A, Lai SH, et al. Epithelioid glioblastomas and anaplastic epithelioid pleomorphic xanthoastrocytomas–same entity or first cousins? Brain Pathol 2016;26(02):215–223
6 Śmiech M, Leszczyński P, Kono H, Wardell C, Taniguchi H. Emerging *BRAF* mutations in cancer progression and their possible effects on transcriptional networks. Genes (Basel) 2020;11;(11):1342
7 Nakagomi N, Sakamoto D, Hirose T, et al. Epithelioid glioblastoma with microglia features: potential for novel therapy. Brain Pathol 2020;30(06):1119–1133
8 Kanemaru Y, Natsumeda M, Okada M, et al. Dramatic response of BRAF V600E-mutant epithelioid glioblastoma to combination therapy with BRAF and MEK inhibitor: establishment and xenograft of a cell line to predict clinical efficacy. Acta Neuropathol Commun 2019;7(01):119
9 Venkatesh A, Joshi A, Allinson K, et al. Response to BRAF and MEK1/2 inhibition in a young adult with BRAF V600E mutant epithelioid glioblastoma multiforme: a case report and literature review. Curr Probl Cancer 2021;45(05):100701
10 Di Nunno V, Gatto L, Tosoni A, Bartolini S, Franceschi E. Implications of BRAF V600E mutation in gliomas: molecular considerations, prognostic value and treatment evolution. Front Oncol 2023;12:1067252
11 Ding Y, Wang Q, Wang F, et al. TTFields prolonged the PFS of epithelioid glioblastoma patient: a case report. Brain Sci 2023;13(04):633
12 Sasame J, Ikegaya N, Kawazu M, et al. HSP90 inhibition overcomes resistance to molecular targeted therapy in BRAFV600E-mutant high-grade glioma. Clin Cancer Res 2022;28(11):2425–2439
13 Liebelt BD, Boghani Z, Takei H, Fung SH, Britz GW. Epithelioid glioblastoma presenting as massive intracerebral hemorrhage: case report and review of the literature. Surg Neurol Int 2015;6(Suppl 2):S97–S100
14 Huang QL, Cao X, Chai X, Wang X, Xiao C, Wang J. The radiological imaging features of easily misdiagnosed epithelioid glioblastoma in seven patients. World Neurosurg 2019;124:e527–e532
15 Wang S, He Q, Zhang Q, Guan B, Zhou X. Clinicopathologic features and prognosis of epithelioid glioblastoma. Int J Clin Exp Pathol 2020;13(07):1529–1539
16 Gaillard F. Epithelioid glioblastoma | Radiology Reference Article | Radiopaedia.org. Radiopaedia. . Doi: 10.53347/rID-45896
17 Zeng Y, Zhu X, Wang Y, et al. Clinicopathological, immunohistochemical and molecular genetic study on epithelioid glioblastoma: a series of fifteen cases with literature review. OncoTargets Ther 2020;13:3943–3952
18 Khanna G, Pathak P, Suri V, et al. Immunohistochemical and molecular genetic study on epithelioid glioblastoma: series of seven cases with review of literature. Pathol Res Pract 2018;214(05):679–685
19 Le BH, Close RA. Imaging and histopathologic nuances of epithelioid glioblastoma. Case Rep Surg 2018;2018:1285729
20 Pan R, Wang X, Fang R, Xia Q, Wu N, Rao Q. Epithelioid glioblastoma exhibits a heterogeneous molecular feature: a targeted next-generation sequencing study. Front Oncol 2022;12:980059
21 Ebrahimi A, Korshunov A, Reifenberger G, et al. Pleomorphic xanthoastrocytoma is a heterogeneous entity with pTERT mutations prognosticating shorter survival. Acta Neuropathol Commun 2022;10(01):5
22 Korshunov A, Chavez L, Sharma T, et al. Epithelioid glioblastomas stratify into established diagnostic subsets upon integrated molecular analysis. Brain Pathol 2018;28(05):656–662
23 Ahmed A, Nobre L, Mason W, et al. Acquired *PTEN* loss may mediate dabrafenib and trametinib resistance in *BRAF* V600E-mutated epithelioid glioblastoma: a case report and literature review. EMJ Oncol Oncol 2023. Doi: 10.33590/emjoncol/10305035
24 Kleinschmidt-DeMasters BK, Aisner DL, Birks DK, Foreman NK. Epithelioid GBMs show a high percentage of BRAF V600E mutation. Am J Surg Pathol 2013;37(05):685–698
25 Simon M, Hosen I, Gousias K, et al. TERT promoter mutations: a novel independent prognostic factor in primary glioblastomas. Neuro-oncol 2015;17(01):45–52
26 Lu VM, George ND, Brown DA, et al. Confirming diagnosis and effective treatment for rare epithelioid glioblastoma variant: an integrated survival analysis of the literature. World Neurosurg 2019;131:243–251.e2
27 Tonse R, Gupta T, Epari S, et al. Impact of WHO 2016 update of brain tumor classification, molecular markers and clinical outcomes in pleomorphic xanthoastrocytoma. J Neurooncol 2018;136(02):343–350
28 Behling F, Barrantes-Freer A, Skardelly M, et al. Frequency of BRAF V600E mutations in 969 central nervous system neoplasms. Diagn Pathol 2016;11(01):55
29 Wan PTC, Garnett MJ, Roe SM, et al; Cancer Genome Project. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell 2004;116(06):855–867
30 Ascierto PA, Kirkwood JM, Grob JJ, et al. The role of BRAF V600 mutation in melanoma. J Transl Med 2012;10(01):85
31 Touat M, Idbaih A, Sanson M, Ligon KL. Glioblastoma targeted therapy: updated approaches from recent biological insights. Ann Oncol 2017;28(07):1457–1472
32 Bouchè V, Aldegheri G, Donofrio CA, et al. BRAF signaling inhibition in glioblastoma: which clinical perspectives? Front Oncol 2021;11:772052
33 Bautista F, Paci A, Minard-Colin V, et al. Vemurafenib in pediatric patients with BRAFV600E mutated high-grade gliomas. Pediatr Blood Cancer 2014;61(06):1101–1103
34 Brown NF, Carter T, Kitchen N, Mulholland P. Dabrafenib and trametinib in BRAFV600E mutated glioma. CNS Oncol 2017;6(04):291–296
35 Zhang J, Yao TW, Hashizume R, et al. Combined $BRAF^{V600E}$ and MEK blockade for $BRAF^{V600E}$-mutant gliomas. J Neurooncol 2017;131(03):495–505
36 Wen PY, Stein A, van den Bent M, et al. Dabrafenib plus trametinib in patients with $BRAF^{V600E}$-mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial. Lancet Oncol 2022;23(01):53–64

