



## Epithelioid Glioblastoma in A 15-Year-Old Boy: A Rare Case Report

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**Abstract:** Epithelioid glioblastoma (E-GBM), one of the rarest intrusive forms of Glioblastoma multiforme (GBM), was consigned in the World Health Organization (WHO) categorization of the Central nervous system (CNS) in the year 2016. The current article reports a rare epithelioid glioblastoma described for its histomorphological character and clinical finding for its medical rarity. The present case deals with a 15-year-old boy complaining of headaches and multiple episodes of vomiting. The investigatory procedures revealed hypo-intense multiple lesions in the left medial frontal lobe extending to a Sylvian fissure. The case is being discussed to distinguish the development of secondary glioblastomas, which usually occur due to pre-existing lesions, which were not present in our discussed case. The patient had come from a rural background with no previous investigations, ophthalmological examination revealed the presence of bilateral papilledema, and the hematological reports were within normal range. The patient was managed with magnetic resonance imaging (MRI) and computed tomography (CT), which depicted a multifocal tumor. Further left fronto temporal craniotomy and ablation of the lesion were done. The surgical procedure upshot divulged that the patient was conscious with improved right side weakness but a remnant motor aphasia, but within a short span, he could walk with support. The incidence of E-GBM that too in adolescent children is minuscule, and due to its poor prognosis, it's very crucial to acknowledge the attributable features of epithelioid glioblastoma, inclusive of functional outset, neuro-imaging, and the hazards of surgical measures.

**Keywords:** Epithelioid Glioblastoma, Histopathology, Immunohistochemistry, Prognosis, BRAFV600E mutation.

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## I. INTRODUCTION

Glioblastoma Multiforme (GBM) is one of the most intrusive diffuse gliomas of astrocytic lineage and is contemplated as a grade IV glioma based on the WHO classification. Of all the gliomas (54%) and primary brain tumors (16%), grade IV astrocytoma is a primary customary malignant primary brain tumor.<sup>1</sup> With a mean survival duration of only fifteen months, GBM endurean incurable tumor. It is essentially detected in an elderly age group with a mean age of approximately 64. The prevalence expands with age culminating at 74 to 84 years, and lessens after 85 years. The age at detection inclines to be elevated for primary GBM with a median age of 55 years than for secondary GBM with a median age of 40.<sup>2</sup> GBM is unconventional in children. Epithelioid glioblastoma (E-GBM), one of the rare contentious GBM forms, was recently consigned in the WHO categorization of the CNS in the year 2016.<sup>3</sup> So also, one more striking feature noted in the currently followed WHO categorization is that it excludes terminology 'multiform' which means that histopathological detection of glioblastoma needs an important affirmation on the diverseness of arrangement of cell unit and tissue structures. Nowadays, many clinicians fail to notice the same defining feature, a varied histological arrangement of cells and tissues 'multiform,' and instead focus on pathological features related to glioblastoma.<sup>4</sup> The common genetic mutation of BRAFV600E amongst various other entities like giant cell glioblastomas, extra-cerebellar pilocyticastrocytomas, and pleomorphic xanthoastrocytomas makes it very challenging to diagnose E-GBM histologically.<sup>5</sup> With the main pathogenesis of frequent leptomeningeal diffusion and clinically poor universal survival of approximately six to seven months, this malignancy captivates the attention of clinicians and surgeons for finding its prognostic cure through neuroimaging, laboratory data sets, and surgical procedures.<sup>6</sup> Besides our understanding of gliomas according to the Batzdorf and Malamud standardized criteria, peculiar discrimination exists among the multicentric gliomas and multifocal tumors, which should be well understood, as both the tumors present at contrasting time intervals. In multicentric gliomas, the tumors emerge in specific sites, and there existsno evidence of radiological connectivity among

the right and left hemispheres, whereas in the case of multifocal tumors, which emerge due to diffusion through cerebrospinal fluid, invasiveness, abide by well-formed commissural tracts and thus a connection exists.<sup>7</sup> The present article reports one multifocal tumor, which is the lofty case of epithelioid GBM (E-GBM) in a 15-yearboy diagnosed accurately based on the WHO categorization (2016) of tumors of the CNS.

## 2. CASE PRESENTATION

### 2.1. Case Report

A 15-year-oldboy came with complaints of headache for15 days and multiple episodes of vomiting for10 days.

### 2.2. Medical history

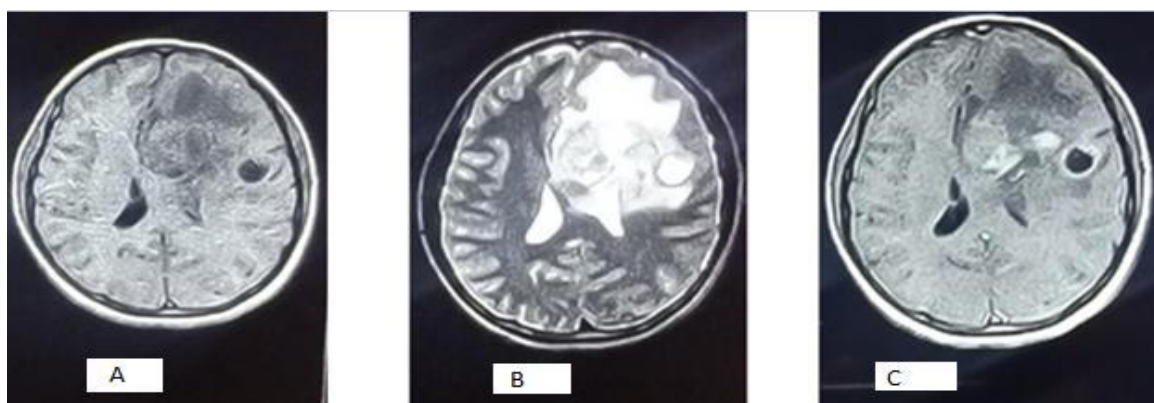
The patient had presented to the health care setup with poor background from a rural area with no previously done investigations.

### 2.3. Family history

The patient's mother was diabetic and hypertensive.

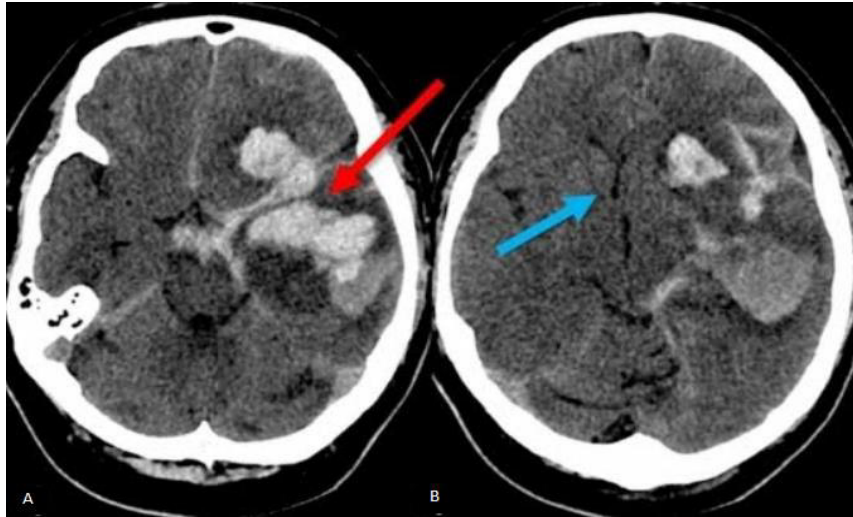
### 2.4. Investigations

On neurological examination, he was consciouswith obeying pupil equally and bilaterally reacting to light; vitals were stable with no focal neurological deficit. On fundus examination, he had papilledema in bilateral eyes. The case was assessed additionally withplain and contrast MRI brain. The T1 weighted visual representation depicted a central hypo-intense multiple lesion in the left medial frontal lobe extending up to the Sylvian fissure, while T2 weighted photomicrograph depicted median hyper-intense gash with hypo-intensity in themargin expressive of an early sub-acute period of blood accumulation with subfalcine herniation (Figure 1). The gadolinium contrast with T1 weighted imaging displayed a large lesion which was 3.2 x 2.8 cm, intensifying solidified substance with other lesions, which was faintly enhanced (Figure 1 B).



**Fig 1. (A, B, C) MRI Brain, T1 and T2 weighted images - A) reveal hypo intense lesion B) Gadolinium contrast imaging revealing 3.2 x 2.8 cm enhancing solid content C) hypo intense multiple lesion in the left medial frontal lobe.**

Based on clinical examination and imaging study, surgery was advised. The patient returned after 15 days in the emergency outpatient department with increased headache, right-sided weakness, and altered sensorium. The patient was evaluated with a non-enhanced CT brain. It revealed that the lesion was increased in size with an increase in perilesional edema and mass effect with midline shifting, as shown in Figure 2 (A, B).



**Fig 2. Non-enhanced CT Scans – A. Showing perilesional edema intruding the basal cisterns (Red arrow). B. Showing perilesional edema with midline shifting (Blue arrow).**

### 2.5. Diagnosis

With the understanding of neuroimaging, a multifocal lesion was detected, enlisting differentials for astrocytoma or glioblastoma.

### 2.6. Intervention

Upon giving general anesthesia, in the supine posture, the patient went through the left frontotemporal craniotomy and ablation of the lesion. After the craniotomy and dural opening, the cerebrum was stretched and protruded out. The growth was not surfacing on the middle frontal gyrus, and the cordectomy tumor specimen was well defined, firm in consistency, and highly vascular gash with no good plain of separation. Near-total (>95%) decompression was done, and a small part of the malignant growth near Broca's area was left behind.

### 2.7. Results

At the end of the surgery, the cerebrum was tense; hence bone flap was not replaced. The action plan was

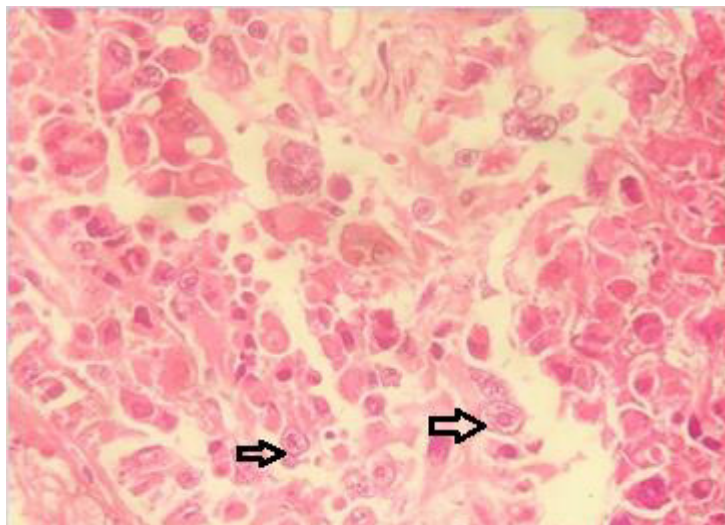
unremarkable, and the patient was transferred to ICU. After the surgery, the patient was conscious with improved right-side weakness but a remnant motor aphasia.

### 2.8. Follow-up

The post-operative sequence was unremarkable, and the patient was dispensed on the 5th postoperative day. During the discharge, the patient had a total right-side auditory loss with right-sided grade IV facial weakness but was in a position to walk without support.

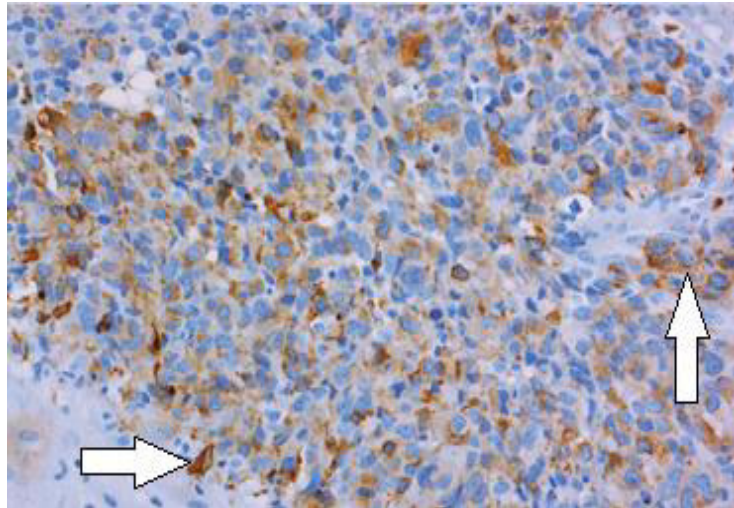
### 2.9. Special tests and investigations

The extracted tissue specimen was sent for histopathological examination. The sections taken from the tumor mass revealed fragments of a high-grade tumor composed of huge necrosis areas and remaining tumor cells arranged throughout the thrombosed and sclerosed vessels. The tumor cells were large pleomorphic with epithelioid morphology and had plentiful eosinophilic cytoplasm and well-defined cytoplasmic borders. The nucleus was vesicular with prominent nucleoli (Figure 3).



**Fig 3: Photomicrograph (Histopathology) Epithelioid glioblastoma – shows large pleomorphic tumor cells with plentiful eosinophilic cytoplasm, with well-defined cytoplasmic borders, vesicular nuclei, and prominent nucleoli, as seen marked by the arrows. (Magnification -H and E – 40x).**

The immunohistochemical analysis was also carried out with the tumor tissue sections, in which the malignant cells displayed cytoplasmic positivity for Glial fibrillary acidic protein (GFAP) (Figure 4) but were negative for Olig2, p53, LICAM, and cytokeratin.



**Fig 4: Photomicrograph (Immunohistochemistry), Epithelioid glioblastoma – malignant cells depicting cytoplasmic positivity [Brown circumscribing granularity] for Glial fibrillary acidic protein (GFAP), as depicted by the arrows.**

### 3. DISCUSSION

Being a rare form of GBM, epithelioid glioblastoma is identified as a tumor that includes a dominant grade diffuse astrocytic tumor form with a presiding population of jointly arranged epithelioid cells, few rhabdoid cells, mitotic activity, micro-vascular augmentation, and necrosis. According to the genetic analyses, approximately 50-95% of all E-GBMs show BRAFV600E mutations and about 70% show TERT promoter mutations. Reports of loss of PTEN are scarce in literature when talking about E-GBM per se. In opposition to the much commoner variant GBM (IDH-1 wild type), this tumor often clinically occurs in persons of younger age group, inclines to display hostile features like metastasis to organs exterior to the CNS, and commonly spreads through cerebrospinal diffusion. With a median age of survival of six months in adults and five months in children, this tumor shows early succession despite the chemotherapies. Only a few isolated reports exist in the literature describing E-GBM since it is challenging to distinguish GBM from its rare variants clinically and based only on genetic mutations. But with the advent of immunohistochemistry, this troubleshooting has been overcome to a certain extent. One such case was discussed by Kohno et al.<sup>8</sup>; where 78-year-old male who was assessed for a slight motor weakness in the right leg. The brain scan revealed tiny stacks in the left frontal and parietal lobes, rapidly increasing for 3 weeks. The surgical excision of the lesion was planned to reach a conclusive detection. Following the excision, the histopathological findings revealed diffuse astrocytoma, but the lesion progressed in size within a short period after surgery. Further biopsy was done, which revealed the diagnosis as epithelioid glioblastoma. Immunohistochemistry depicted lesion was negatively stained for p53 and cytokeratin but was positively stained for Glial fibrillary acidic protein. A similar case was referred by Liebelt et al.<sup>9</sup> who had studied a 66-year-old American African woman who had a history of insidious headaches, which was followed by right-sided weakness and drowsiness. Her neuroimaging reports depicted a lobulation with magnifying extravasating mass in the anterior temporal lobe encompassed by vasogenic edema. After the tumor excision,

the immunohistochemistry details revealed that the malignant cells were positive for GFAP and negative for HMB 45, pan-cytokeratin, and p53. This conclusion was drawn that the lesion may be diagnosed as E-GBM, mainly with immunohistochemistry. The study conducted by Zeng et al.<sup>10</sup> took into account fifteen cases of E-GBM. The principal symptom the patients presented was headache and blurring of vision. The microscopic images of all the cases revealed that the malignant cells comprised epithelioid cells and a few rhabdoid cells. These cells displayed focal discontinuation, minimal interceding neuropil, a prominent membrane, eosinophilic cytoplasm, and aneccentrically placed nucleus. Most of the tumors taken as samples depicted increased mitosis, focal necrosis, and microvascular proliferation. The immunohistochemistry revealed that the epithelioid cells were positive for GFAP and vimentin. EGFR mutations and BRAFV600E mutations were also recorded in ten out of fifteen cases. Some other studies, including as carried out by Mishra et al.<sup>11</sup>, Woo et al.<sup>12</sup>, Akimoto et al.<sup>13</sup>, Nakajima et al.<sup>14</sup>, and Louis et al.<sup>15</sup> had similar observations inculcating immunohistochemistry and histopathology of E-GBM as discussed in our study. Considering the other variants like intraventricular epithelioid glioblastomas, Nitta et al.<sup>16</sup> discussed a peculiar case of a 47-year-old woman who had presented with an intraventricular mass, with already existing and concurrent low-grade tumor which depicted a pre-existing calcified lesion on CT. And it was analyzed by the study that even after the intervention on day 33, the patient expired, plus the combinations of mutations along with BRAFV600E might have led to the conversion of IDH-wild type low-graded glioma in the direction of epithelioid glioblastoma. In contrast, our study depicted perilesional edema on CT rather than any calcification with no pre-existing or concurrent low-grade tumor. After the intervention, the patient survived, and the right weakness was improved with only remnant motor aphasia. And mostly, BRAFV600E mutation was depicted in our research. The combinations of findings were discussed in the study of Broniscer et al.<sup>17</sup>, where a CT scan, which was taken before the detection of the malignancy, revealed an abnormal zone with much calcification. The CT at the time of recognition of

malignancy revealed the same calcification enclosed by the tumor, which concluded that secondary epithelioid glioblastoma might co-exist with calcification. This finding differed from our research since the CT findings were not revealed before discovering the lesion. Few other observations recorded by Kleinschmidt et al.<sup>5</sup> Khanna et al.<sup>18</sup>, and Korshunov et al.<sup>19</sup> mainly focused on molecular alterations involving BRAFV600E mutations, TERT promoter mutation, and other differentials of E-GBM. The study of Wang et al.<sup>20</sup> followed up on a total of 33 cases suspected of epithelioid glioblastoma, in which it was revealed almost 100% (33 cases) had BRAFV600E mutation, similar to our study and 54.5% (18 cases) of them depicted TERT mutation. The main agenda of their study was to find the perfect basis for clinical diagnosis and prognosis of E-GBM using molecular studies. The research study carried out by Lu et al.<sup>21</sup> updated us with the fact that despite carrying out the study on 59 cases of E-GBM, the histological detection of it doesn't stray from the clinical course of the wide glioblastoma diagnosis despite being a distinct histologic entity. Sugimoto et al.<sup>22</sup> studied four cases and concluded that most patients suffered lepto-meningeal dissemination, worsening the prognostication. This was contradictory to our study case since there was no diffusion involved. Moreover, the author emphasized that molecular targeted drug therapy such as BRAF inhibition must occur shortly. The present study primarily focused on neuroimaging, histopathology, and immunohistochemistry related to E-GBM, with the main intention of investigating the peculiar neurological case in an adolescent, which is rarely reported.

#### 4. CONCLUSION

Although very sparsely reported in the literature, E-GBM, an

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uncommon variant of GBM, is a well-documented entity with histomorphological epithelioid features and poor prognosis. Epithelioid glioblastoma must be contemplated in the distinctive detection of multiple tumors due to its ability for extremely truculent and powerful insinuating characteristics. The clinicians should be more alert with preoperative neuroimaging details associated with this lesion. Also, formal genetic studies inculcating BRAFV600E and TERT mutations must be necessary for precise diagnosis and apt treatment.

#### 5. ETHICAL APPROVAL STATEMENT

Written consent was taken from the patients parents to conduct and publish the study.

#### 6. ACKNOWLEDGEMENTS

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#### 7. AUTHOR'S CONTRIBUTION STATEMENT

Dr. Parth Shah gathered the data and all the details of the patient. Then, Dr. Hanish Chawda analyzed and gave the necessary inputs to prepare the case. All the authors have read and agreed to the whole of the manuscript.

#### 8. CONFLICT OF INTEREST

Conflict of interest declared none.

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