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Case Report

Epithelioid glioblastoma presenting as multicentric glioma: A case report and review of the literature

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ABSTRACT

Background: Epithelioid glioblastoma is a rare aggressive variant of glioblastoma multiforme (GBM), which was formally recognized by the World Health Organization classification of the central nervous system in 2016. Clinically, epithelioid GBMs are characterized by aggressive features, such as metastases and cerebrospinal fluid dissemination, and an extremely poor prognosis. A rare case of epithelioid GBM that was discovered as a multicentric glioma with different histopathology is reported.

Case Description: A 78-year-old man was admitted to our hospital with mild motor weakness of the right leg. Neuroimaging showed small masses in the left frontal and parietal lobes on magnetic resonance imaging. The abnormal lesion had been increasing rapidly for 3 weeks, and a new lesion appeared in the frontal lobe. 11C-methionine positron emission tomography (PET) showed abnormal uptake corresponding to the lesion. To reach a definitive diagnosis, surgical excision of the right frontal mass lesion was performed. Histological findings showed diffuse astrocytoma. Only radiotherapy was planned, but the left frontal and parietal tumors progressed further within a short period. Therefore, it was thought that these tumors were GBM, and a biopsy of the left parietal tumor was performed. The histological diagnosis was epithelioid GBM. Immunohistochemistry showed that most tumor cells were negatively stained for p53 and isocitrate dehydrogenase 1. *BRAF* V600E mutations were not identified, but *TERT* promoter mutations were identified. Immediately after surgery, the patient was given chemotherapy using temozolomide, extended local radiotherapy and then bevacizumab. After 6 months, he showed no signs of recurrence.

Conclusion: Epithelioid GBM is one of the rarest morphologic subtypes of GBM and has a strongly infiltrative and aggressive nature. Therefore, careful identification of preoperative imaging studies and detailed evaluation of genetic studies are necessary to select the appropriate treatment for epithelioid GBM.

Keywords: Bevacizumab, *BRAF* V600E mutation, Epithelioid glioblastoma, Multicentric glioma, *TERT* promoter mutation

INTRODUCTION

Epithelioid glioblastoma multiforme (GBM) is one of the rarest aggressive GBM variants and was newly proposed in the World Health Organization (WHO) classification of the central nervous

system (CNS) in 2016.[13] This tumor entity is characterized by frequent leptomeningeal dissemination and poor overall survival of approximately 6 months.[2,6,10,12,13,16] Therefore, it is very important to recognize the characteristic features of epithelioid GBM, including the type of clinical onset, laboratory data, neuroimaging, and the risks of surgical procedures. A rare case of epithelioid GBM occurring as a multicentric GBM that was diagnosed precisely based on the 2016 WHO classification of tumors of the CNS is presented, and the diagnostic pitfalls and useful indicators for the accurate diagnosis of this rare tumor are presented.

CASE DESCRIPTION

A 78-year-old man presented to our department with mild motor weakness of the right leg. Magnetic resonance imaging (MRI) of the brain demonstrated small masses in the left frontal and parietal lobes [Figure 1a]. The abnormal lesion had been increasing rapidly for 3 weeks, and a new lesion appeared in the frontal lobe [Figure 1b]. All of the tumors on MRI findings showed high intensity on diffusion-weighted imaging (DWI), and they were homogeneously enhanced to a high degree with gadolinium (Gd) [Figure 1b and c]. However, there was no hyperintense connection between the left hemisphere lesions and the right frontal lobe tumor on fluid-attenuated inversion recovery. 11C-methionine PET showed abnormal uptake corresponding to the lesion. The maximum standardized uptake values were left frontal mass 5.28, left parietal mass 4.76, and right frontal mass 2.83 [Figure 1d]. Laboratory examinations, including cerebrospinal fluid studies, showed no abnormal findings, and the concentrations of tumor markers remained with normal limits. To confirm the histological diagnosis, surgical gross total resection of the right frontal lesion was performed by craniotomy. Histological findings obtained from hematoxylin and eosin staining of the tumor showed diffuse astrocytoma, and the tumor cells showed negative immunostaining for R132H-mutated isocitrate dehydrogenase-1 (*IDH-1*), P53, and phosphatase and tensin homolog deleted from chromosome 10 (PTEN). The Ki-67 (MIB-1) proliferation-related labeling index was low, at 4.0% [Figure 2a and b]. Given the pathological results, only radiotherapy without chemotherapy was planned, but the remaining left frontal and parietal tumors progressed further within a short period [Figure 2c]. Therefore, it was thought that these tumors were malignant glioma, such as GBM, and a biopsy of the left parietal tumor was performed. Histological diagnosis showed highly cellular and medium-sized rounded cells with abundant eosinophilic cytoplasm and laterally

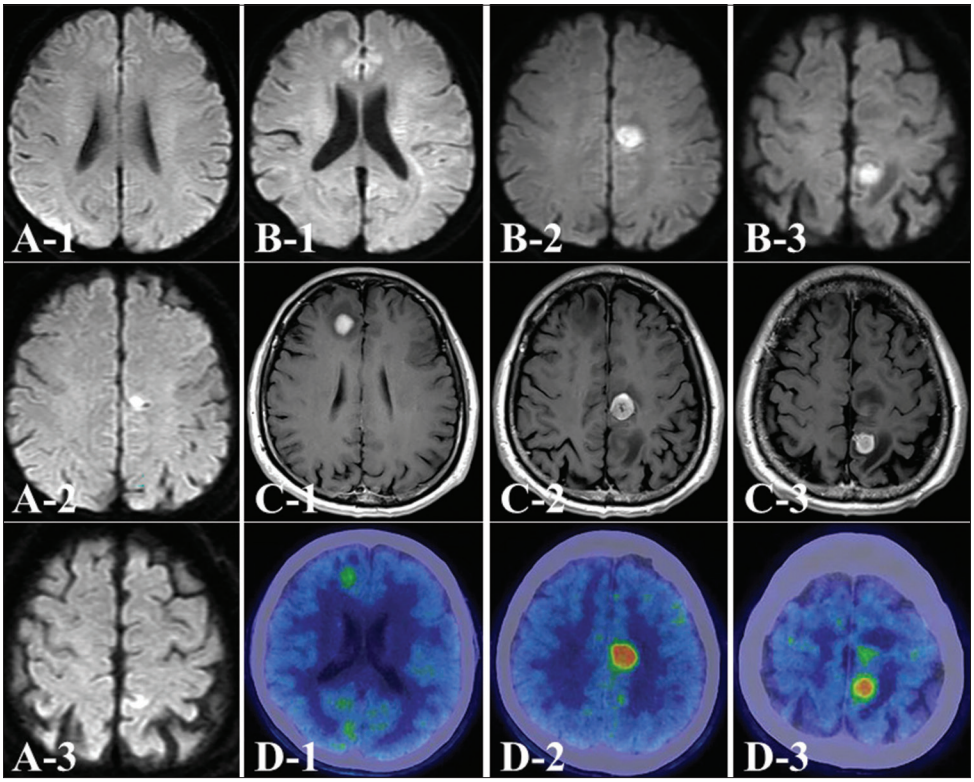

Figure 1: Preoperative axial diffusion-weighted image (DWI) on magnetic resonance imaging shows a high-intensity mass in the left hemisphere (a). These masses are rapidly growing, and a new lesion appears in the right frontal lobe (b). These tumors in accordance with the DWI high-intensity lesion are homogeneously enhanced to a high degree with gadolinium (c). The maximum standardized uptake values on methionine positron emission tomography are high (d).

positioned nuclei [Figure 3a]. On immunohistochemical examinations, glial fibrillary acidic protein (GFAP) and integrase interactor 1 (INI-1) staining were observed in epithelioid cells [Figure 3b and c]. In addition, O6-methylguanine-methyltransferase immunoreactivity of tumor cell nuclei was also observed at the positive rate of 76.3%. However, most tumor cells were negatively stained for p53, PTEN, and R132H-mutated *IDH-1*. The MIB-1 labeling index was high, at 40.0% [Figure 3d]. *BRAF* V600E mutations were not identified, but *TERT* promoter mutations were recognized (C250T: c.−146C>T) [Figure 3e]. Taking all these results into account, the final diagnosis was epithelioid GBM in accordance with the 2016 WHO Classification of Tumors of the CNS. Immediately after surgery, the patient was treated with chemotherapy using temozolomide (TMZ) (75 mg/m^2) and extended local radiotherapy (40 Gy/15 fractions). Nevertheless, after the administration of TMZ at 3 weeks, the tumors showed further growth on MRI [Figure 4], and the symptom of right hemiparesis worsened apparently, so bevacizumab was added at this point. There were then no signs of recurrence, and MRI at 10 months after initial treatment showed marked size reduction and disappearance of peritumoral hyperintense lesions [Figure 5]. In addition, the patient's neurological findings returned to near normal.

DISCUSSION

Epithelioid GBM is one of the rarest variants of GBM, and it was formally recognized in the 2016 WHO classification.[13] The definition of this tumor included a high-grade diffuse astrocytic tumor variant with a dominant population of closely packed epithelioid cells, some rhabdoid cells, mitotic activity, microvascular proliferation, and necrosis.[13] Genetic analyses show *BRAF* V600E mutation in 50–93% of all epithelioid GBMs. *TERT* promoter mutations have been reported at a high percentage (70%). A loss of PTEN has occasionally been reported.[9,13,17] Clinically, this tumor often occurs in young patients and tends to present with aggressive features, such as metastases to organs outside the CNS and cerebrospinal fluid dissemination, as opposed to common GBM (*IDH-1* wild type).[2,6,10,12,13,16] It demonstrates early progression, with a median survival of 6.3 months (range: 0.6–82 months) in adults and 5.6 months (range: 1.5–9.7 months) in children, despite adjuvant therapies.[13] In the present case, the patient was relatively old, at 78 years of age, which was atypical for epithelioid GBM. Thus, in cases demonstrating aggressive features, even in an elderly patient, it is important to suspect the possibility of epithelioid GBM.

In terms of imaging characteristics, preoperative identification of this tumor may be difficult with radiological examinations. In general, epithelioid GBM characteristically presents as a Gd-enhancing solid mass, occasionally with cysts. These tumors are prone to hemorrhage and often spread through the leptomeninges.[13] In the present case, all three tumors were seen as high-intensity masses on DWI, in addition to showing strong contrast enhancement by Gd. This high-intensity distribution on DWI is extremely interesting and seems to be the key finding for the preoperative diagnosis of epithelioid GBM.

A recent report based on integrated molecular analysis proposed that epithelioid GBM should be stratified into three subsets: a PXA subset, with a high percentage of *BRAF* V600E mutations, but a relatively low percentage of *TERT* promoter mutations; an adult *IDH*-wild-type GBM subset, with a relatively low percentage of *BRAF* V600E mutations, but a high percentage of *TERT* promoter mutations; and a pediatric RTK1 subset not harboring either mutation.[11] Histologically, the current case presented with many epithelioid cells showing monotonous and highly cellular, medium-sized, round cells with variably centrally to eccentrically positioned nuclei. This structure was immunopositive for GFAP, S-100, and INI-1 and immunonegative for p53 and PTEN. With regard to the genetic profile, *BRAF* V600E mutations were not seen, but *TERT* promoter mutation was confirmed. These findings are consistent with epithelioid GBM (adult *IDH*-wild-type GBM subset), given the results of the morphological, immunohistochemical, and genetic studies; therefore, this tumor was diagnosed as epithelioid GBM, in accordance with the WHO classification.[13]

With respect to the definition of multicentric gliomas, Batzdorf and Malamud reported criteria to distinguish multifocal tumors from multicentric tumors.[1,7,14,15] Multifocal tumors develop due to invasion or growth that follows established routes such as commissural or tract fibers, or they can also occur by dissemination through cerebrospinal fluid channels or local metastasis. In contrast, multicentric gliomas occur in multiple sites distant to each other, as in different lobes or hemispheres, with no connecting pathways between them.[1,7,14,15] It has also been emphasized that these two types of tumors occur at different times. In the present case, the tumors arose in three different locations of the left and right hemispheres (left frontal, left parietal, and right frontal lobes), and there was no evidence on MRI of macroscopic connectivity between the left and right regions. Furthermore, the right frontal tumor appeared to have arisen at a different time. Although local intracerebral metastasis could not be completely excluded from the differential diagnosis, a diagnosis of multicentric gliomas was made due to their differing findings on histological examination. Previously, Kuroda *et al*. reported a case of an epithelioid GBM colocalized with a low-grade diffuse astrocytoma.[12] However, our case is multicentric glioma occurred in different region and demonstrated different pathological findings. Therefore, this present case is extremely rare and represents the first report related to the pathophysiology of epithelioid GBM.

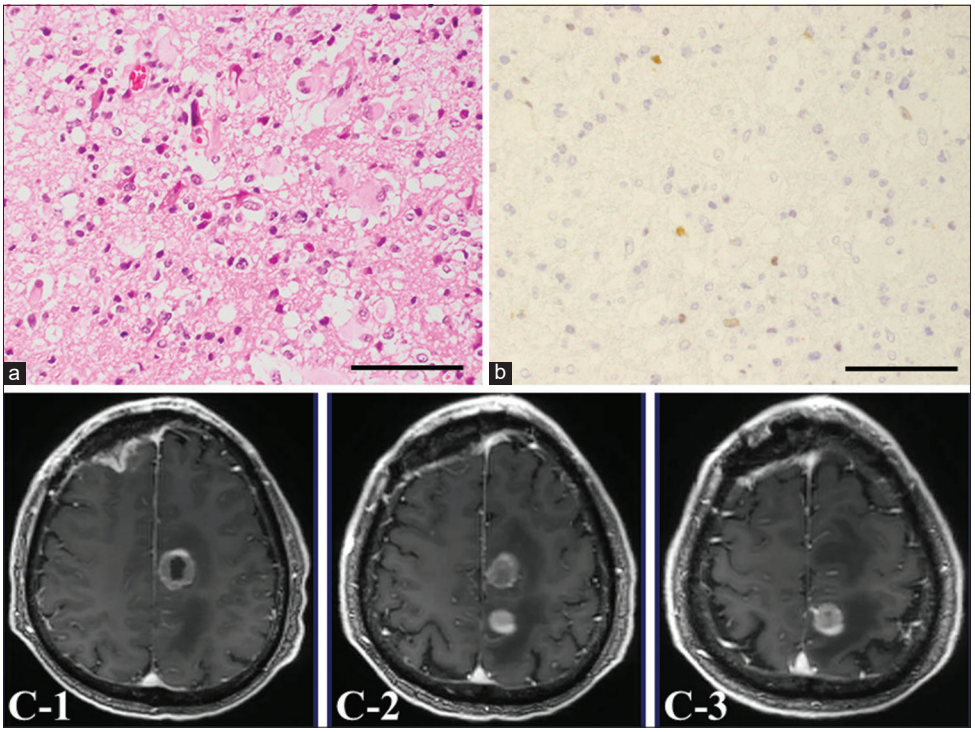

Figure 2: Histopathology of the resected frontal tumor (a) shows diffuse astrocytoma. This tumor shows slightly positive staining for Ki-67 (b). Postoperative axial gadolinium-enhanced T1-weighted magnetic resonance imaging (c) demonstrates rapid growth within a short period. Magnification (a and b), ×400. Scale bar, 100 μm.

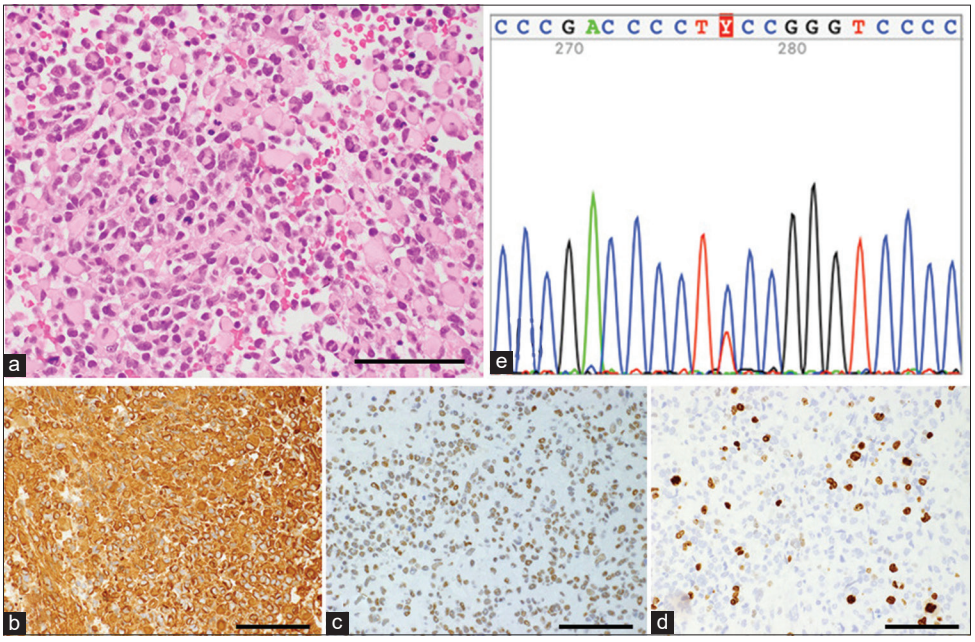

Figure 3: Histopathology of the left parietal tumor. Hematoxylin and eosin staining (a) shows highly cellular and medium-sized rounded cells. Immunohistochemical examinations showing glial fibrillary acidic protein (b), integrase interactor 1 staining (c), and high Ki-67 labeling index (d). Magnification (a-d), ×400. Scale bar, 100 μm. Direct DNA sequence using Sanger method detects *TERT* promoter mutation (C250T: c.−146C>T) (e).

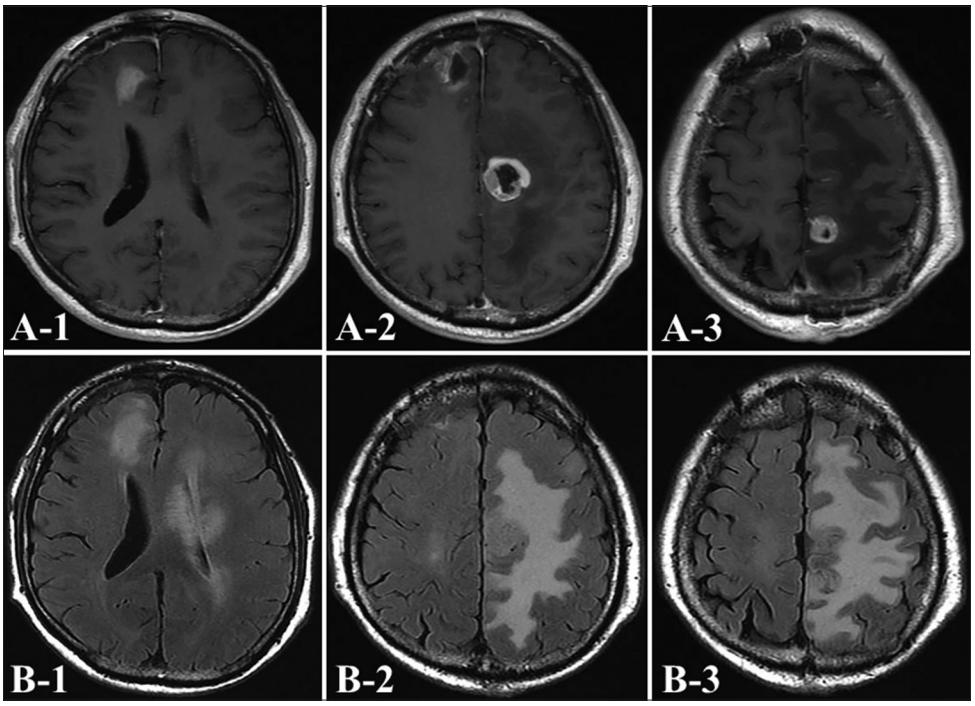

Figure 4: Images from postchemoradiotherapy axial gadolinium-enhanced T1-weighted imaging (a) and fluid-attenuated inversion recovery magnetic resonance imaging (b) demonstrating the residual tumors growing further, and the peritumoral edema is worse.

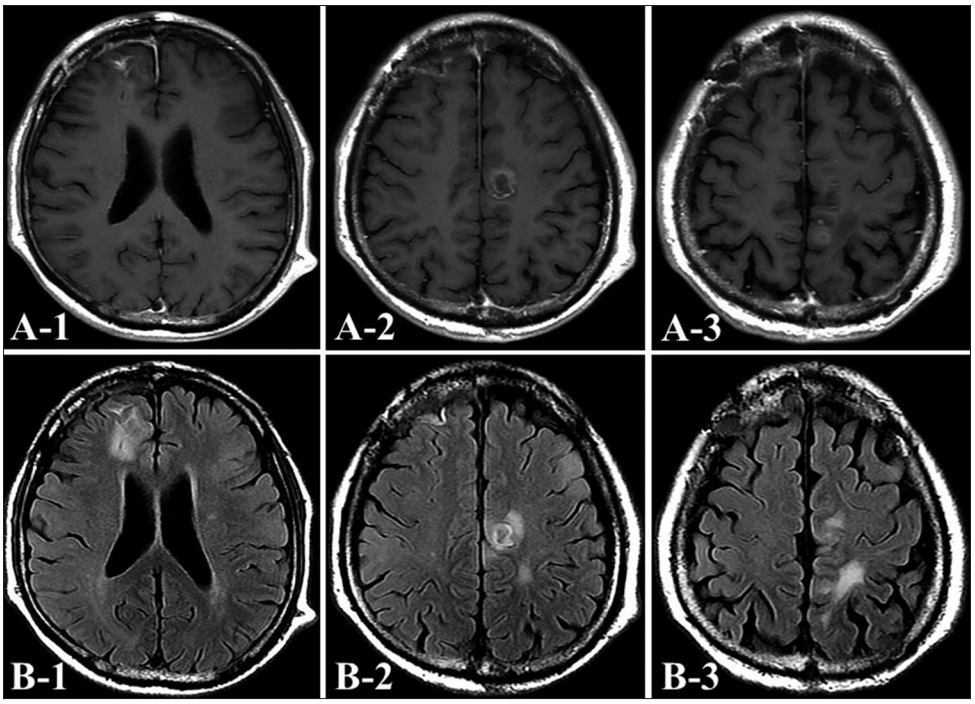

Figure 5: Axial gadolinium-enhanced T1-weighted imaging (a) and fluid-attenuated inversion recovery (b) magnetic resonance imaging at 10 months after administration of bevacizumab has clearly decreased in size and peritumoral edema.

Finally, with regard to the adjuvant therapy, the administration of bevacizumab was extremely effective in the present case. Recently, several case reports have described the success of targeted treatment using BRAF inhibitors and MEK inhibitors to *BRAF* V600E-mutant epithelioid GBM.[8,18] However, in our case, *BRAF* V600E mutations were not identified unfortunately. Bevacizumab is a humanized recombinant monoclonal antibody targeting vascular endothelial growth factor (VEGF)

receptor. However, two large randomized trials have failed to demonstrate an overall survival benefit of VEGF blockade by bevacizumab in the adjuvant therapy of patients with newly diagnosed GBM.[3-5] In the present case, bevacizumab was given immediately after the primary chemoradiotherapy because the rapid progression of the tumor was not stopped by TMZ and extended radiotherapy, resulting in excellent tumor control at 10 months of follow-up without neurological complications and no apparent recurrence. The administration of bevacizumab with chemoradiotherapy using TMZ may be an effective, less-invasive treatment for epithelioid GBM in multiple regions. Further, experience with this therapy and longer patient follow-up are required.

CONCLUSION

Epithelioid GBM is a very rare, but well-documented entity. Epithelioid GBM should be considered in the differential diagnosis of multiple tumors due to its potential for highly aggressive and strong infiltrative features. Therefore, careful preoperative imaging with DWI/MRI and detailed evaluation of genetic studies including *BRAF* V600E and *TERT* promoter mutation are necessary for accurate diagnosis and appropriate selection of treatment for epithelioid GBM.

Declaration of patient consent

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

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Nil.

Conflicts of interest

There are no conflicts of interest.

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