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ORIGINAL ARTICLE

Clinicopathological characteristics and treatment outcomes of epithelioid glioblastoma

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Abstract

Epithelioid glioblastoma is a new variant of glioblastoma that has been recently recognized in the 2016 WHO classification of brain tumors. Given the rarity of epithelioid glioblastoma, the clinical characteristics, pathological features, radiological findings, and treatment outcomes are still not well characterized. Therefore, we identified eighty-four epithelioid glioblastoma cases to investigate these characteristics and identify the possible prognostic factors of survival. There were 55 male and 29 female patients with a mean age of 33.6 years. Headache (77.3%) was the most common clinical symptom, and other common symptoms included nausea or vomiting (34%), dizziness (20.5%), seizures (13.6%), and limb weakness (13.6%). Most lesions (88.1%) were located in cerebral lobes, especially in the frontal lobe and temporal lobe. One hundred percent of the patients were IDH1 wild-type (75/75) and INI-1 positive (58/58), and 57.3% (47/82) of patients harbored $BRAF^{V600E}$ mutation. The median overall survival (OS) of all patients was 10.5 months. Patients who received chemotherapy ($p = 0.006$) or radiotherapy ($p = 0.022$) had a longer survival than patients who did not. In addition, the K-M curve showed that the $BRAF^{V600E}$ mutation status was not associated with survival ($p = 0.724$). These findings may assist clinicians with better understanding and management of epithelioid glioblastoma.

Keywords Epithelioid glioblastoma · Clinicopathological characteristics · $BRAF^{V600E}$ mutation · Prognosis

Introduction

Glioblastoma is the most common primary malignant brain tumor and accounts for approximately 48% of primary malignant brain tumors [43], with a median survival of 14.6 months through current standard treatment of surgery plus concurrent chemoradiotherapy [36, 53]. Based on its morphological diversity and cellular heterogeneity, three uncommon variants of glioblastoma have been described, including giant cell glioblastoma, gliosarcoma, and epithelioid glioblastoma [31, 32]. Epithelioid glioblastoma is recognized as a new variant of glioblastoma and classified as a subtype of IDH wild-type glioblastoma in the 2016 World Health Organization (WHO) classification of brain tumors [32]. Histologically, it is characterized by monotonous, closely packed large epithelioid, melanoma-like cells with laterally positioned nuclei, prominent nucleoli, abundant eosinophilic cytoplasm, distinct cellular membranes, and lack of cytoplasmic stellate processes [1, 22, 32, 45]. Furthermore, $BRAF^{V600E}$ mutation is found in nearly half of epithelioid glioblastomas, which is significantly higher when compared with conventional glioblastoma [3, 5, 23, 47]. Clinically, epithelioid glioblastoma tends to occur in young patients and often shows aggressive behaviors such as cerebrospinal fluid dissemination and extra-central nervous system (CNS) metastasis, which is different from conventional glioblastoma [5, 38].

It has been reported that epithelioid glioblastoma accounts for approximately 3% of all glioblastomas [44, 63]. Given the rarity of epithelioid glioblastoma, most of the published reports about epithelioid glioblastoma are either case reports or small case series so far [21, 26, 55, 63]. Previously, Lu et al. [33] searched the literature and performed an integrated survival analysis of epithelioid glioblastoma. However, the included cases in their study were confused between epithelioid glioblastoma and rhabdoid glioblastoma. Rhabdoid glioblastoma is another rare pattern of glioblastoma that has not been added into the WHO classification of brain tumors and can be distinguished from epithelioid glioblastoma by focal loss of

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INI1 protein in rhabdoid areas and polyphenotypic immunohistochemical expression [22]. To date, the clinical characteristics, pathological features, radiological findings, and treatment outcomes of epithelioid glioblastoma are still not well characterized. Therefore, we conducted a systematic search of the literature about epithelioid glioblastoma to investigate these characteristics and identify the possible prognostic factors of survival.

Materials and methods

Case selection

We retrospectively reviewed glioma patients treated at the Department of Neurosurgery in West China Hospital between 2016 and 2019 and identified eight newly diagnosed epithelioid glioblastoma patients. We also systematically searched the literature published in English language about epithelioid glioblastoma from Web of Science and PubMed and ultimately identified seventy-six eligible cases with available clinical and survival data from twenty-four articles. The key terms used for search strategy were "epithelioid" and "glioblastoma." Meanwhile, the reference lists of included articles were also reviewed. The eligible cases met the following inclusion criteria: (1) the definite diagnosis of epithelioid glioblastoma was made; (2) the lesion was located in the brain; (3) basic clinical data and accurate survival data were available. When dealing with duplicated cases reported by the same author or institution, only the cases with more complete and updated data were selected. In addition, several reports using the terms "epithelioid glioblastoma" and "rhabdoid glioblastoma" interchangeably were excluded [2, 54]. This study was approved by the Ethics Committee of West China Hospital. Informed consent form for all included cases in our institution was obtained.

Data collection

Basic clinical data of our eight cases were extracted from our hospital information system and survival data were obtained from telephone interview. Data of reviewed cases were extracted from the texts, tables, and figures of the included articles. We recorded age, gender, clinical manifestation, radiological features, surgical treatment, adjuvant therapy, and survival data. In addition, available immunohistochemical staining results and molecular features such as P53 expression status, vimentin, epithelial membrane antigen (EMA), IDH1 mutation, INI1 loss, $BRAF^{V600E}$ mutation, TERT promoter mutation, ATRX deletion, and MGMT promoter methylation were also collected.

Statistical analysis

SPSS software version 21.0 was used for data statistics and analysis. Continuous variables were presented as means and standard deviations or median and ranges, while categorical variables were presented as numbers and percentage. During data analysis, the median values of continuous variables were considered as cutoff values. Tumor diameter was divided into dichotomous variables. Age was divided into two groups: children group (< 18 years) and adult group (≥ 18 years). Survival analysis was performed twice with and without age stratification using Kaplan-Meier curves and tested by a log-rank test. Two-tailed p value < 0.05 was considered statistically significant.

Results

Patient demographics and clinical characteristics

A total of 84 cases, including 76 cases identified from 24 articles and 8 cases from our institution, were included in this study. The details and summary of patient demographics and clinical characteristics are shown in Table 1 and Table 2. There were 55 male and 29 female patients, giving a male-to-female ratio of 1.9:1. The mean age was 33.6 ± 20.3 years and the median age was 30 years (range 2–79 years). Eighteen (21.4%) patients were children and 66 (78.6%) patients were adults. Seventy-eight patients were diagnosed with primary epithelioid glioblastomas, and six patients were diagnosed with secondary epithelioid glioblastoma. Of six secondary epithelioid glioblastomas, three cases were arising from pleomorphic xanthoastrocytoma, two cases were arising from anaplastic astrocytoma, and the other one was arising from grade III glioma (not available glioma type). Among 44 patients with available clinical symptoms, headache (77.3%) was the most common clinical symptom, and other common symptoms included nausea or vomiting (34%), dizziness (20.5%), seizures (13.6%), and limb weakness (13.6%).

In terms of tumor location, most lesions (88.1%) were located in cerebral lobes. The frontal lobe (39.3%) and temporal lobe (35.7%) were most often involved, followed by the parietal lobe (22.6%) and occipital lobe (10.7%). For lesions not located in cerebral lobes, four lesions were located in the thalamus, one in the hypothalamus, two in the lateral ventricle, one in the corpus callosum, and two in the cerebellum. In addition, the distribution of tumor was at the left side (43.5%), the right side (51.6%), midline (1.6%), and bilateral side (3.2%). The mean diameter of all available tumors was 4.6 ± 1.5 cm, with a median diameter of 4.7 cm (range 1.5–9.2 cm). In terms of surgical modalities for the patients with available surgical data, the majority of them (97.1%, 67/69) received surgical resection and two patients received only

Table 1 Literature review of epithelioid glioblastoma

Case number	Reference	Age (years)	Sex	Clinical manifestation	Tumor location	Diameter (cm)	Surgical treatment	Radio	Chemo	MGMT methylation	$BRAF^{V600E}$ mutation	OS (months)
1	Kuroda et al. 2016 [26]	26	F	Nausea for several days	Right frontal lobe	NA	GTR	Yes	Yes	No	Yes	2.2, dead
2	Funata et al. 2016 [13]	30	M	Headache, nausea, and vomiting for 2 weeks	Right frontal lobe, basal ganglia, and thalamus	NA	Resection	Yes	Yes	NA	Yes	9.6, alive
3	Nakajima et al. 2018 [38]	21	M	NA	Temporoparietal lobe	NA	Resection	Yes	Yes	NA	Yes	7, dead
4		32	M	NA	Parietal lobe	NA	Resection	Yes	Yes	NA	Yes	10, alive
5		70	M	NA	Parietal lobe	NA	Resection	Yes	Yes	NA	Yes	7, dead
6		23	M	NA	Frontal lobe	NA	Resection	Yes	Yes	NA	Yes	3, dead
7		32	F	NA	Occipital lobe	NA	Resection	Yes	Yes	NA	Yes	26, alive
8		47	M	NA	Parietal lobe	NA	Resection	Yes	Yes	NA	No	25, dead
9	Smith-Cohn et al. 2019 [51]	49	M	A history of anaplastic astrocytoma for 2 years	Right temporal lobe	NA	STR	Yes	Yes	NA	Yes	8, dead
10	Tosuner et al. 2018 [57]	44	M	NA	Parietal lobe	NA	NA	NA	NA	NA	Yes	10.1, alive
11		2	M	NA	Frontotemporal lobe	NA	NA	NA	NA	NA	No	6.2, dead
12		49	M	NA	Frontal lobe	NA	NA	NA	NA	NA	No	13.2, alive
13		17	F	NA	Parietal lobe	NA	NA	NA	NA	NA	No	7, alive
14	Zeng et al. 2020 [63]	45	M	A history of anaplastic astrocytoma for 5 years	Left temporal-occipital lobe	4	Resection	No	No	No	Yes	5, dead
15		32	M	Headache for 1 month	Left temporal lobe	5.3	Resection	No	No	No	No	12, dead
16		32	F	Headache and sudden disturbance of consciousness	Right frontal lobe	4.3	Resection	No	Yes	No	Yes	8, dead
17		52	M	Dizziness and headache for 10 h	Right temporal lobe	3	Resection	No	No	No	No	3, dead
18		18	F	Nausea and vomiting for 3 weeks, limb weakness and palpitation for 2 days	Left thalamus	2.8	Resection	No	No	No	No	0.2, dead
19		40	M	Dizziness and headache for 8 months, aggravation and vomiting for 1 month	Left occipital lobe	5	Resection	Yes	No	Yes	Yes	15, dead
20		44	M	Dizziness, headache, and vomiting for 4 days	Right frontal lobe	3	Resection	Yes	Yes	Yes	Yes	32, dead
21		20	M	Dizziness and headache for 3 months, aggravation and vomiting for 1 month	Right temporal lobe	3.2	Resection	No	No	No	Yes	15, dead
22		34	M	Dizziness and headache for 1 year accompanied by double vision of left eye for half a month	Right frontal lobe	6.5	Resection	No	No	No	No	0.5, dead
23		77	M	Weakness of left limb for 1 month	Left temporal lobe	5.5	Resection	No	No	Yes	No	0.5, dead
24		29	M	Dizziness for 4 days, aggravation and vomiting for 2 days	Right frontal lobe	9.2	Resection	Yes	Yes	Yes	Yes	7, dead
25		58	M	Dizziness for 1 year	Left frontal and temporal lobe	4.8	Resection	No	No	Yes	No	3, alive
26		25	M	Headache for 1 month	Right temporal and occipital lobe	4	Resection	No	Yes	Yes	Yes	2, alive
27		32	F	Headache for half a month	Right frontal and temporal lobe	5	Resection	No	No	No	No	1, alive
28		56	M	Headache for 3 months and abnormal speech for 2 weeks	Right frontal and parietal lobe	3.5	Resection	No	No	Yes	No	9, dead
29	Broniscer et al. 2014 [5]	10	F	NA	Thalamus	NA	Resection	Yes	Yes	NA	Yes	4.8, dead
30		11	M	NA	Temporal lobe	NA	NTR	Yes	No	NA	Yes	3.9, dead
31		10	F	NA	Bilateral thalamic	NA	NA	Yes	No	NA	Yes	1.4, dead
32		3	M	NA	Frontal lobe	NA	NTR	Yes	Yes	NA	No	6.5, dead
33		3	F	NA	Hypothalamic	NA	NA	Yes	Yes	NA	No	7.7, dead
34		5	M	NA	Thalamus	NA	Resection	Yes	No	NA	No	9.7, dead

Table 1 (continued)

Case number	Reference	Age (years)	Sex	Clinical manifestation	Tumor location	Diameter (cm)	Surgical treatment	Radio	Chemo	MGMT methylation	$BRAF^{V600E}$ mutation	OS (months)
35	Furuta et al. 2018 [14]	71	M	NA	Right parietal lobe	NA	NA	NA	NA	NA	Yes	3.2, dead
36		32	F	NA	Left occipital lobe	NA	NA	NA	NA	NA	Yes	34.2, alive
37		10	F	NA	Left parietal lobe	NA	NA	NA	NA	NA	No	12, dead
38		11	F	NA	Left frontal lobe	NA	NA	NA	NA	NA	No	15, alive
39		79	M	NA	Cerebellum	NA	NA	NA	NA	NA	No	4, alive
40		19	M	A history of pleomorphic xanthoastrocytoma	Left frontal lobe	NA	NA	NA	NA	NA	Yes	9, dead
41	Tanaka et al. 2014 [55]	25	F	A history of pleomorphic xanthoastrocytoma for 13 years, headache, and focal seizure	Left temporal lobe	NA	STR	Yes	Yes	No	Yes	4.3, dead
42	Matsumura et al. 2017 [34]	18	M	Headache for 1 month	Right temporal lobe	6.5	PR	Yes	Yes	NA	Yes	4, dead
43	Kanemaru et al. 2019 [20]	57	M	Headaches and slight dysphasia.	Left frontal lobe	6	STR	Yes	Yes	NA	Yes	8, dead
44	Finneran et al. 2018 [12]	29	F	Headaches for 2 weeks and partial seizures	Left temporal lobe	1.5	GTR	Yes	No	No	No	6, alive
45	Kohno et al. 2020 [24]	78	M	Mild motor weakness of the right leg	Right frontal lobe, left frontal lobe, and left parietal lobe	NA	GTR and biopsy	Yes	Yes	No	No	10, alive
46	Alexandrescu et al. 2016 [1]	11	M	NA	Right temporoparietal lobe	NA	GTR	NA	NA	NA	Yes	65, alive
47		79	M	NA	Right temporal lobe	NA	NA	NA	NA	NA	No	8, alive
48		70	F	NA	Right temporal lobe	NA	NA	NA	NA	NA	No	5.2, alive
49		12	M	NA	Frontal lobe	NA	STR	NA	NA	NA	No	14, dead
50		11	M	NA	Temporal lobe	NA	STR	NA	NA	NA	Yes	38, alive
51		2	M	NA	Lateral ventricle	NA	GTR	NA	NA	NA	Yes	16, alive
52		14	M	NA	Parietal lobe	NA	GTR	NA	NA	NA	No	33, alive
53		56	M	NA	Right temporal lobe	NA	NA	NA	NA	NA	NA	2, alive
54	Nakagomi et al. 2020 [37]	20	F	Headache and continuous vomiting for 1 month	Frontal lobe	NA	Resection	Yes	No	NA	Yes	2, dead
55	Miyahara et al. 2016 [35]	42	M	Headache and mild aphasia for 2 weeks	Left parietal lobe	NA	GTR	No	No	NA	Yes	3, dead
56	Nitta et al. 2018 [39]	47	F	Headache and nausea for 40 days	Right lateral ventricle	NA	PR	No	No	NA	Yes	1.1, dead
57	Nobusawa et al. 2014 [40]	22	M	Headache	Right occipital lobe	NA	STR	Yes	Yes	NA	Yes	24, alive
58	Woo et al. 2019 [62]	22	F	Headache for 3 months	Right temporal lobe	3.6	NTR	Yes	Yes	Yes	Yes	7, dead
59		22	M	Headache for 2 months	Right frontal lobe	5.8	STR	Yes	Yes	Yes	Yes	7.5, dead
60	Leaver et al. 2016 [29]	26	M	Headache, vomiting, and memory problems	Right temporal lobe	NA	GTR	No	Yes	NA	Yes	1.3, dead
61	Werner et al. 2019 [61]	60	M	Attention deficits	Corpus callosum	5.7	Biopsy	Yes	Yes	Yes	No	11, dead
62	Le et al. 2018 [28]	27	M	Onset of tonic-clonic seizure	Right temporal-parietal lobe	4.7	Resection	Yes	Yes	No	Yes	3, alive
63	Khanna et al. 2018 [21]	47	F	Headache, seizures, and vomiting	Right frontotemporal lobe	NA	GTR	NA	NA	NA	Yes	5, alive
64		30	M	Headache, seizures, and altered sensorium	Left frontal lobe	NA	GTR	NA	NA	NA	No	4, alive
65		35	M	Headache and vomiting	Left frontotemporal lobe	NA	GTR	NA	NA	NA	No	2, alive
66		18	F	Headache and vomiting	Left Temporoparietal lobe	NA	GTR	NA	NA	NA	Yes	3, alive
67		50	F	Left-sided weakness and headache	Right frontal lobe	NA	GTR	NA	NA	NA	No	3, alive
68		13	M	Headache and seizures	Right frontotemporal lobe	NA	GTR	NA	NA	NA	No	4, alive
69		14	F	Headache and vomiting	Left frontal lobe	NA	GTR	NA	NA	NA	No	6, alive
70		24	M	NA	Right temporal lobe	NA		NA	NA	NA	No	5.8, dead

Table 1 (continued)

Case number	Reference	Age (years)	Sex	Clinical manifestation	Tumor location	Diameter (cm)	Surgical treatment	Radio	Chemo	MGMT methylation	$BRAF^{V600E}$ mutation	OS (months)
	Kleinschmidt-DeMasters et al. 2013 [23]						Biopsy and resection					
71		27	F	NA	Left occipital lobe	NA	Resection	NA	NA	NA	Yes	76.5, alive
72		18	M	NA	Right frontoparietal lobe	NA	Resection	NA	NA	NA	No	62.3, alive
73		25	M	NA	Cerebellar hemisphere	NA	Resection	NA	NA	NA	No	15.4, dead
74		43	M	NA	Left temporal-parietal lobe	NA	Resection	NA	NA	NA	Yes	6.1, dead
75		69	M	NA	Left frontal lobe	NA	Biopsy	NA	NA	NA	No	19.8, dead
76		10	F	NA	Right parietooccipital lobe	NA	Biopsy and resection	NA	NA	NA	Yes	40.1, dead
77	Our cases	43	F	Headache and left limb weakness for 2 weeks	Right frontal lobe, basal ganglia, and lateral ventricle	5	STR	No	No	Yes	Yes	2, dead
78		33	M	A history of pleomorphic xanthoastrocytoma for 2 years	Left frontal lobe	4	GTR	Yes	Yes	No	Yes	11, dead
79		40	F	Headache, dizziness, nausea, and vomiting for 1 month	Left frontal lobe	5	GTR	Yes	Yes	Yes	Yes	10.5, dead
80		61	F	Right limb weakness for 10 days	Left parietal lobe	3.8	GTR	Yes	Yes	NA	No	5.2, dead
81		54	F	Dizziness and headache for 1 month	Left frontal lobe	4.7	GTR	No	Yes	No	NA	21.1, dead
82		19	M	Headache for 2 weeks	Left temporal lobe	3	GTR	Yes	Yes	No	Yes	3.2, alive
83		47	F	A history of grade III glioma for 10 years and walking unsteadily for 6 months	Left parietal and occipital lobe	6.3	GTR	Yes	Yes	NA	Yes	38.1, dead
84		55	M	Headache and memory decline for 20 days	Right frontal lobe	4.6	GTR	Yes	Yes	Yes	Yes	12.1, alive

Table 2 Summary of patient demographics and clinical and radiological features

Characteristic	*N* (%)
Age, years	
< 18	18 (21.4)
18–65	58 (69)
≥ 65	8 (9.5)
Median	30 (range 2–79)
Mean and SD	33.6 ± 20.3
Sex	
Male	55 (65.5)
Female	29 (34.5)
Clinical symptoms	
Headache	34/44 (77.3)
Dizziness	9/44 (20.5)
Nausea or vomiting	15/44 (34)
Seizures	6/44 (13.6)
Limb weakness	6/44 (13.6)
Tumor location	
Frontal lobe	24 (28.6)
Temporal lobe	18 (21.4)
Parietal lobe	10 (11.9)
Frontoparietal lobe	2 (2.4)
Frontotemporal lobe	6 (7.1)
Temporoparietal lobe	4 (4.8)
Parietooccipital lobe	2 (2.4)
Temporooccipital lobe	2 (2.4)
Occipital lobe	5 (6.0)
Thalamus	4 (4.8)
Hypothalamic	1 (1.2)
Lateral ventricle	2 (2.4)
Corpus callosum	1 (1.2)
Multicentric lesion	1 (1.2)
Cerebellum	2 (2.4)
Tumor side	
Left	27 (43.5)
Right	32 (51.6)
Bilateral	2 (3.2)
Midline	1 (1.6)
Tumor diameter (cm)	4.6 ± 1.5
Radiotherapy	
Yes	35 (67.3)
No	17 (32.7)
Chemotherapy	
Yes	33 (63.5)
No	19 (36.5)

biopsy. In addition, among 52 patients with available adjuvant treatment data, 35 (67.3%) patients received radiotherapy and 33 (63.5%) received chemotherapy.

Immunohistochemical results and molecular features

The summary of available immunohistochemical results and molecular features is shown in Table 3. One hundred percent of the patients were IDH1 wild-type (75/75) and INI-1 positive (58/58), whereas 7.3% (3/41) showed EGFR amplification and no one (0/26) showed 1p/19q deletion. Detection of $BRAF^{V600E}$ mutation was performed in 82 patients and 47 (57.3%) patients were mutant. P53 expression status was available in 66 patients and half of them were positive. MGMT promoter was methylated in 44.8% (13/29) of patients, TERT promotor mutation was detected in 52% (26/50) of patients, and ATRX loss was observed in 4.1% (2/49) of patients. CDKN2A/B deletion, PTEN deletion, and H3K27M mutation were found in 66.7% (14/21), 15.4% (4/26), and 2.7% (1/37) of patients, respectively. In addition, vimentin was positive in 97.6% (40/41) of patients and epithelial membrane antigen (EMA) was positive in 41.1% (23/56) of patients.

Survival outcome and prognosis analysis

The median overall survival (OS) of all patients was 10.5 months. In the survival analysis without age stratification shown in Table 4, there was no difference in survival between the genders ($p = 0.967$). The children group had a median OS of 12 months, and the adult group had a median OS of 9 months. However, the difference was not statistically significant ($p = 0.156$). Tumor location, tumor side, and tumor diameter were found to have no significant impact on OS. Patients who received chemotherapy ($p = 0.006$) or radiotherapy ($p = 0.022$) had a longer survival than patients who did not (Fig. 1). MGMT promoter methylation did not have an effect on patient survival ($p = 0.606$). In addition, the K-M curve showed that the $BRAF^{V600E}$ mutation status was not associated with survival ($p = 0.724$). Also, results from the survival analysis using age stratification were consistent with those of unstratified analysis.

Discussion

Epithelioid glioblastoma is a rare subtype of IDH wild-type glioblastoma that has been recently recognized in the 2016 WHO classification of brain tumors [32]. It is noteworthy that epithelioid glioblastoma is distinguished from glioblastoma with epithelial metaplasia, which displays epithelial differentiation with squamous nests, glandular structures, and immunohistochemical expression of specific epithelial markers [45]. Histologically, epithelioid glioblastoma predominantly comprised discohesive sheets of epithelioid cells, and variably presents rhabdoid cells [1, 22, 32, 45]. The epithelioid cells are large round cells with laterally positioned nuclei, prominent

Table 3 Available IHC results and molecular features of epithelioid glioblastoma and conventional glioblastoma [8, 25, 47, 48, 50, 56]

Molecular type	Epithelioid glioblastoma, *N* (%)	Conventional glioblastoma
IDH1 wild-type	75/75 (100)	5%
INI-1 positive	58/58 (100)	NA
$BRAF^{V600E}$ mutation	47/82 (57.3)	2%
P53 positive	33/66 (50)	47%
MGMT promotor methylation	13/29 (44.8)	50%
ATRX loss	2/49 (4.1)	4%
TERT promotor mutation	26/50 (52)	72%
CDKN2A/B deletion	14/21 (66.7)	NA
H3K27M mutation	1/37 (2.7)	3%
PTEN deletion	4/26 (15.4)	25%
EGFR amplification	3/41 (7.3)	40%
1p/19q deletion	0/26 (0)	5%
EMA positive	23/56 (41.1)	NA
Vimentin positive	40/41 (97.6)	NA

nucleoli, abundant eosinophilic cytoplasm, distinct cellular membranes, and lack of cytoplasmic stellate processes [1, 22, 32, 45]. Typical features of conventional glioblastoma, including necrosis, microvascular proliferation, and elevated mitotic activity, are also frequently seen [1, 21, 38, 63]. Unlike pleomorphic xanthoastrocytoma or other glioneuronal tumors, eosinophilic granular bodies and Rosenthal fibers are rarely seen in epithelioid glioblastoma [1, 14, 21, 22, 34].

It has been reported that epithelioid glioblastoma accounts for approximately 3% of all glioblastomas [44, 63]. Unlike conventional glioblastoma which is often diagnosed at older ages [43], this study showed that epithelioid glioblastoma tended to occur in children and young adults. The children group accounted for 21.4% of all included epithelioid glioblastomas, whereas the elderly group accounted for only 9.5%. The median age of all patients at diagnosis was 30

Table 4 Survival analysis using log-rank test

Age stratification	Variable	*n*	$\chi 2$	*p* value
All age group	Age, < 18/≥ 18 (years)	18/66	2.008	0.156
	Sex, male/female	55/29	0.002	0.967
	Tumor side, left/right/others	27/32/3	0.109	0.947
	Tumor location, cerebral lobe/others	74/10	2.650	0.104
	Tumor diameter, ≤ 4.7/> 4.7 (cm)	16/14	0.229	0.632
	Chemotherapy, yes/no	33/19	7.486	**0.006**
	Radiotherapy, yes/no	35/17	5.207	**0.022**
	MGMT methylation, yes/no	13/16	0.266	0.606
	$BRAF^{V600E}$ mutation, yes/no	47/35	0.124	0.724
Age < 18 (years)	Sex, male/female	10/8	0.110	0.741
	Tumor location, cerebral lobe/others	13/5	2.443	0.118
	$BRAF^{V600E}$ mutation, yes/no	7/11	0.190	0.663
Age ≥ 18 (years)	Sex, male/female	45/21	0.092	0.761
	Tumor side, left/right/others	24/29/2	0.587	0.745
	Tumor location, cerebral lobe/others	61/5	1.340	0.247
	Chemotherapy, yes/no	30/16	6.803	**0.009**
	Radiotherapy, yes/no	29/17	7.145	**0.008**
	$BRAF^{V600E}$ mutation, yes/no	40/24	0.266	0.606

Statistically significant differences are highlighted in bold

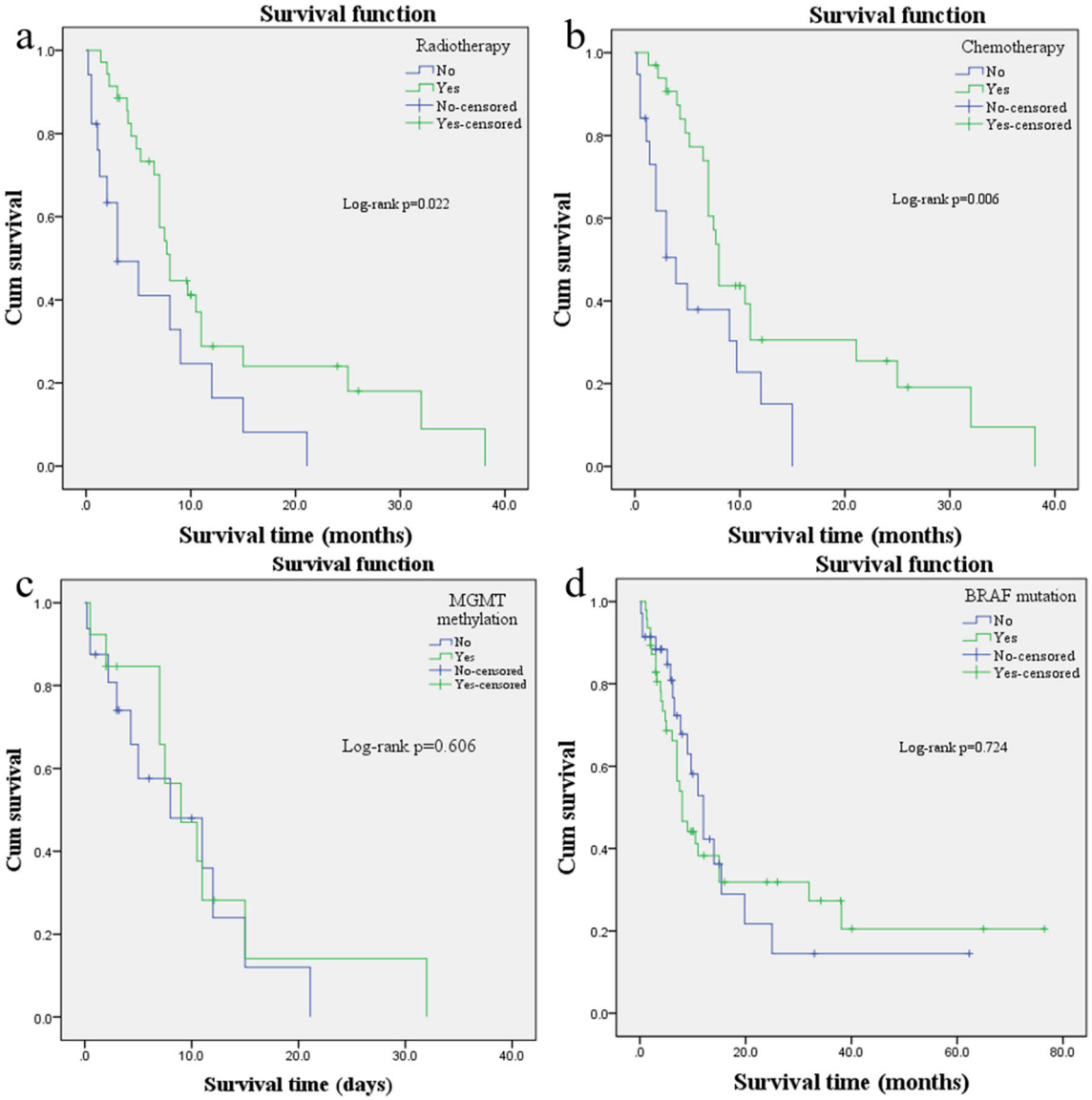

Fig. 1 Kaplan-Meier survival analysis. **a** Relationship between radiotherapy and survival outcome ($p = 0.022$). **b** Relationship between chemotherapy and survival outcome ($p = 0.006$). **c** Relationship between MGMT methylation and survival outcome ($p = 0.606$). **d** Relationship between BRAF mutation and survival outcome ($p = 0.724$)

years, which is apparently younger than conventional glioblastoma with a median age of 65 years at diagnosis [43]. In addition, epithelioid glioblastoma had a predilection for males and the gender ratio of male-to-female was approximately 2:1. As far as clinical manifestations are concerned, there were no specific symptoms or signs. Headache was the most common clinical symptom, and other main symptoms included nausea or vomiting, dizziness, seizures, and limb weakness.

In terms of tumor location, epithelioid glioblastoma was mainly located in cerebral lobes, especially in the frontal lobe and temporal lobe. A few cases located in the thalamus [5, 63], hypothalamus [5], lateral ventricle [1, 39], cerebellum [14, 23], and spinal cord [1] also have been reported in the literature. There was a slight difference between left-sided and right-sided distribution, with a left-right ratio of 1:1.2. Radiologically, epithelioid glioblastoma often appeared as single superficially located, well-circumscribed, heterogeneously enhanced or ring enhanced mass [12, 18, 19, 22, 63]. Occasionally, it manifests as multifocal or multicentric lesions [15, 24]. More particularly, dura matter attachment, which is known to be common in meningioma, can sometimes be shown on enhanced magnetic resonance imaging of epithelioid glioblastoma [14, 18, 22, 63]. In such cases, epithelioid glioblastoma may be misdiagnosed as meningioma. As shown in Fig. 2 (illustrated case 81), MRI revealed a well-circumscribed and markedly enhanced lesion with dura matter attachment in the left frontal lobe and it was initially diagnosed with meningioma.

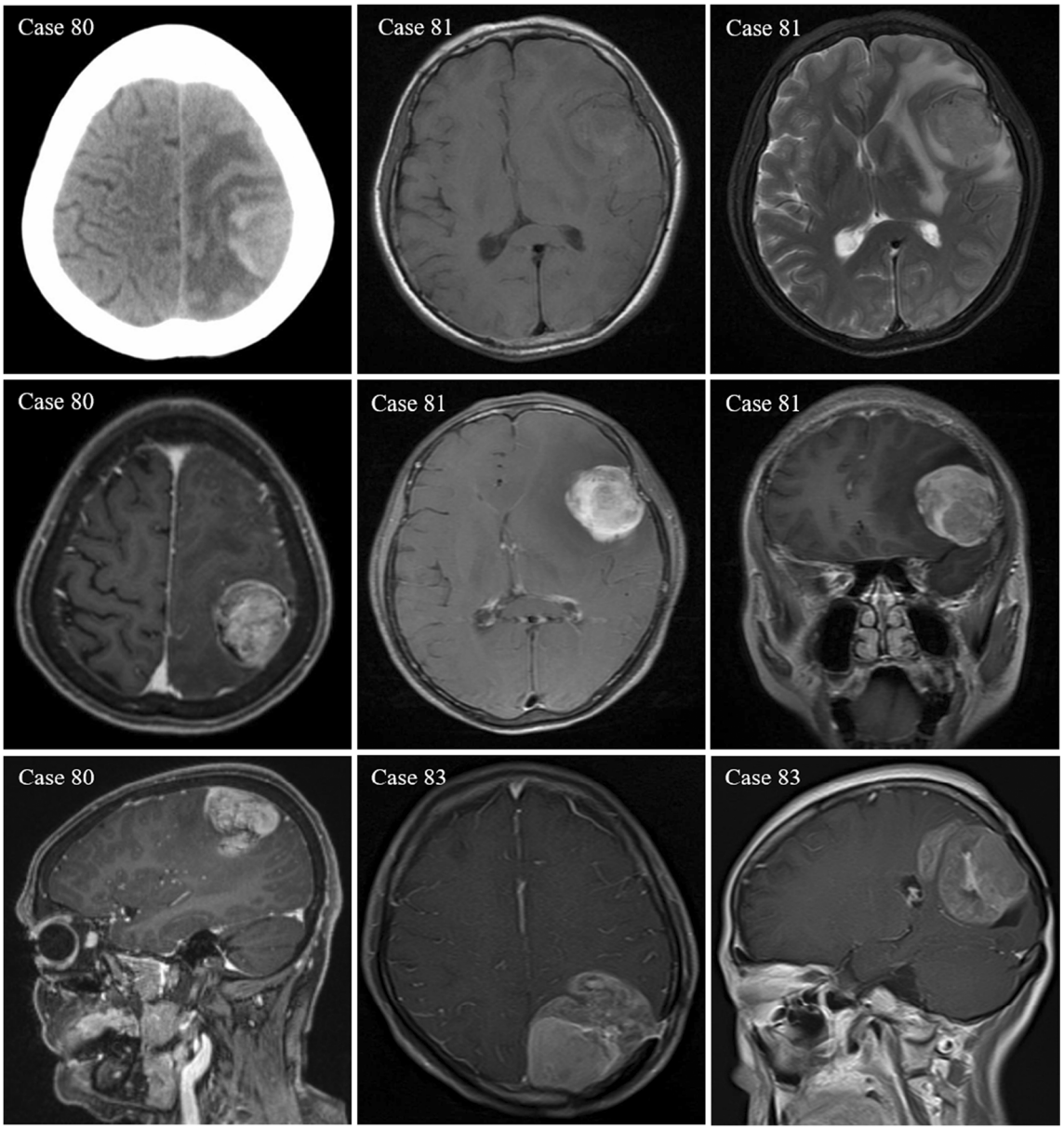

Fig. 2 Imaging characteristics of three illustrated cases from our institution. Epithelioid glioblastoma appeared as a superficially located, well-circumscribed, and markedly enhanced mass with dura matter attachment on MRI images

Calcification, an important imaging characteristic of oligodendroglial tumors [52], can also be seen in epithelioid glioblastoma. In this study, five cases (cases 1, 2, 31, 55, and 56) showed calcification on CT scans. Interestingly, in case 31 and case 56, CT scans obtained 3 years before diagnosis showed abnormal areas with obvious calcification and CT scans performed at diagnosis showed the same calcification within the tumor. It suggested that abnormal areas may be the precursor lesions of epithelioid glioblastoma. In addition, the presence of coexisting lower grade glioma-like components with epithelioid glioblastoma has been reported in nine cases: diffuse astrocytoma-like components in six cases [26, 34, 38, 40], an anaplastic astrocytoma-like component in one case [38], an oligoastrocytoma-like component in one case [13], and an pleomorphic xanthoastrocytoma–like component in one case [38]. Furthermore, six out of 84 cases had a history of lower grade glioma in this study. Taking together, these findings suggested that epithelioid glioblastoma may develop from lower grade glioma through malignant transformation in some cases, and did not merely occur as primary or de novo lesions.

$BRAF^{V600E}$ mutation, which can constitutively activate MAPK/ERK signaling pathway, has been detected in many different tumors, including approximately 60% of melanoma [9], 33% of papillary thyroid carcinoma [11], 12% of

colorectal cancer [10], and 2% of non-small cell lung carcinoma [7]. This mutation has also been found in several types of brain tumors, including pleomorphic xanthoastrocytomas (66%), gangliogliomas (18%), and pilocytic astrocytomas (9%), but rarely found in conventional glioblastoma (approximately 2%) [47]. Conversely, several studies suggested that nearly half of epithelioid glioblastomas harbored $BRAF^{V600E}$ mutation [5, 23]. In this study, $BRAF^{V600E}$ mutant epithelioid glioblastoma accounted for 57.3% of all cases. This finding suggested that $BRAF^{V600E}$ mutation may serve as an auxiliary diagnostic biomarker for epithelioid glioblastoma. Moreover, one hundred percent of the cases were IDH1 wild-type and INI-1 was retained in all cases. Methylation of MGMT promoter was observed in 44.8% of cases and ATRX loss was observed in 4.1% of cases, which is similar to conventional glioblastoma [50, 56]. However, epithelioid glioblastoma showed a lower frequency of TERT promotor mutation (52%) and PTEN loss (15.4%) than conventional glioblastoma [50]. In addition, EGFR amplification was uncommon in epithelioid glioblastoma [1, 5, 21, 63], and only 7.3% of cases showed EGFR amplification in this study, which is significantly lower than in conventional glioblastoma (approximately 40%) [50]. Notably, no 1p/19q was found in any case of this study.

Epithelioid glioblastoma often showed aggressive behaviors such as cerebrospinal fluid dissemination and extra-CNS metastasis [1, 5, 38], which is distinctly different from conventional glioblastoma. The metastatic sites reported in the literature included the scalp, parotid gland, liver, lung, thoracic wall, lymph node, vertebral body, and peritoneum [5, 38, 40, 51]. Interestingly, two extra-CNS metastatic cases through a VP shunt were reported by Broniscer et al. [5], one was scalp metastasis and the other was peritoneal metastasis. Additionally, intratumoral hemorrhage, although relatively uncommon in glioma [41, 58], often occurred in epithelioid glioblastoma [5, 18]. In this study, nine cases (cases 1, 29, 30, 32, 41, 42, 56, 57, and 70) were described to have intratumoral hemorrhage. Several studies believed that discohesiveness of tumor cells and invasion into the vascular wall may be related to cerebrospinal fluid dissemination, extra-CNS metastasis, and intratumoral hemorrhage [26, 38].

Previous studies demonstrated that epithelioid glioblastoma had a particular poor prognosis [5, 38, 62]. This study showed that the median OS of epithelioid glioblastoma was 10.5 months, which is close to that reported by Wang et al. [59]. However, it is significantly shorter than that of conventional glioblastoma (14.6 months) [53]. It has been suggested that high-grade gliomas with leptomeningeal spread generally have a shorter survival [4]. Therefore, we speculated that such aggressive behaviors of epithelioid glioblastoma may be one cause of poor prognosis.

As is well known, surgery is the cornerstone in the initial treatment of glioblastoma [36, 60]. Many studies have reported that the extent of resection in glioma surgery had an obvious effect on patient survival, and greater extent of resection was associated with improved overall survival [6, 17, 49]. In this study, the majority of the cases received surgical resection and two cases received only biopsy. Due to the limited cases with available data on extent of resection, extent of resection was not included in survival analysis, and more cases are needed to evaluate its effect on survival of epithelioid glioblastoma in the future. In addition, adjunct therapies including radiotherapy and chemotherapy have been demonstrated to be helpful for prolonged survival of glioblastoma [53]. Likewise, this study showed that both radiotherapy and chemotherapy were significantly associated with improved overall survival. These results indicated that epithelioid glioblastoma also benefited from standard chemotherapy and radiotherapy for conventional glioblastoma. Moreover, an interesting case of BRAF wild-type epithelioid glioblastoma going through complete regression on imaging after radiotherapy plus chemotherapy has been recently reported [61]. Regrettably, only 67.3% of patients received radiotherapy and 63.5% of patients received chemotherapy in this study. Based on available information, case 44 refused chemotherapy for unknown reason and sought nutritional therapy. Case 60 was complicated by steroid-induced psychosis and incapable of receiving radiotherapy. Case 77 refused radiotherapy and chemotherapy due to poor economic conditions and case 81 was afraid of side effects of radiotherapy. Such reasons tell us that enhancing patients' understanding of the disease and chemoradiotherapy may help to increase the proportion of patients receiving chemoradiotherapy and thus improve prognosis.

MGMT promoter methylation status has emerged as an important prognostic factor in glioblastoma [16, 42]. It is known that MGMT methylation is associated with better prognosis and better response to temozolomide [16, 42]. However, MGMT methylation was found to have no significant impact on OS in this study. Given the small number of cases analyzed, future studies with a large number of cases are still needed to evaluate its effect on prognosis of epithelioid glioblastoma. $BRAF^{V600E}$ mutation has been reported to be associated with poor prognosis in some tumors, including papillary thyroid carcinoma, melanoma, and colorectal cancer [30, 46]. Given the high $BRAF^{V600E}$ mutation rate and poor prognosis of epithelioid glioblastoma, we doubted whether $BRAF^{V600E}$ mutation was a bad biomarker for overall survival. Therefore, $BRAF^{V600E}$ mutation was included in the survival analysis and it showed no difference in survival between wild-type and mutant $BRAF^{V600E}$ epithelioid glioblastoma. Previously, one study indicated that $BRAF^{V600E}$ mutation was related to poor prognosis in pediatric low-grade gliomas [27], while another study by Zhang et al. [64] demonstrated that this mutation was a favorable prognostic

factor in young adult glioblastoma patients. At present, the prognostic value of $BRAF^{V600E}$ mutation in glioma remains controversial and more studies are needed to investigate its prognostic impact on glioma.

Limitations

This study has several limitations. Firstly, this study was a retrospective analysis and most cases were reviewed from published case reports and case series, which could lead to selection or publication bias. Secondly, the sample size was relatively small, which results in low statistical power and may limit the universality of these findings. Thirdly, immunohistochemical results may be unconvincing due to lack of unified standards. In addition, subgroup analysis stratified by extent of resection and Karnofsky performance status was unable to be performed due to limited cases with available related data.

Conclusions

Epithelioid glioblastoma is a rare subtype of IDH wild-type glioblastoma. In this study, we summarized clinical characteristics, imaging findings, histopathological features, and genetic alterations of epithelioid glioblastoma and identified the prognostic factors of survival. These findings may assist clinicians with better understanding and management of epithelioid glioblastoma.

Author contribution Study conception and design: KJS and YHL. Data acquisition: KJS, XWZ, TFL, MRZ, and JHL. Analysis and interpretation of data: KJS and XWZ. Statistical analysis: KJS and XWZ. Manuscript preparation and editing: KJS and YHL.

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Data availability Data will be made available on request.

Code availability Not applicable.

Declarations

Ethics approval This study was approved by the Ethics Committee of West China Hospital.

Consent to participate Informed consent form for all included cases in our institution was obtained.

Consent for publication All authors approved the manuscript to be published.

Conflict of interest The authors declare no competing interests.

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