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CLINICAL STUDY

Diffuse astrocytic glioma, IDH-Wildtype, with molecular features of glioblastoma, WHO grade IV: A single-institution case series and review

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Abstract

Objective In 2018, cIMPACT-NOW update 3 concluded that WHO grade II/III IDH-wildtype diffuse astrocytomas that contain *TERT* promoter mutations, chromosome 7 gain/10 loss, and/or *EGFR* amplification, correspond to a WHO grade IV diagnosis and should be classified as *Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV* (DAG-G). We present a single-institution series of patients with DAG-G and IDH-mutant astrocytomas and compare their clinical, molecular, and radiographic characteristics.

Methods Patient data was retrospectively extracted from the EMR for all patients undergoing surgical biopsy/resection of a diffuse astrocytoma at our institution from 2018 to 2020. Clinical presentation, molecular alterations, radiographic appearance, surgery, and survival were reviewed for each patient.

Results Six DAG-G patients were identified in our cohort. All patients had diffuse disease, and presented with expansile, T2 hyperintense lesions with minimal enhancement. Compared to patients with classic IDH-mutant astrocytomas, mean age for DAG-G patients was older (68 vs 33 years, $p < 0.0001$), tumors were more diffuse ($p = 0.02$), with patients more likely to present with focal deficits and receive a biopsy only ($p = 0.005$). Overall survival was significantly shorter for DAG-G patients ($p = 0.03$).

Conclusion Patients with DAG-G are more likely to be older than typical IDH-mutant diffuse astrocytoma patients. They are more likely to present with tumors in a diffuse pattern with focal deficits. When such patients are encountered, prompt biopsy/resection to confirm the diagnosis and immediate initiation of adjuvant therapy is recommended, as the disease progression and overall prognosis is similar to glioblastoma.

Keywords Astrocytoma · Glioblastoma · Diffuse astrocytic glioma · IDH-wildtype

Abbreviations

ATRX	Alpha-thalassemia/mental retardation syndrome X-linked
cIMPACT-NOW	The consortium to inform molecular and practical approaches to CNS tumor taxonomy
CNS	Central nervous system

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DAG-G	Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV
EGFR	Epidermal growth factor receptor
FLAIR	Fluid attenuation inversion recovery
GBM	Glioblastoma
GTR	Gross-Total resection
IDH	Isocitrate dehydrogenase
MGMT	O-6-Methylguanine-DNA methyltransferase
MRI	Magnetic resonance imaging
OS	Overall survival
PFS	Progression-free survival
PTEN	Phosphatase and Tensin homolog
STR	Sub-Total resection
TERT	Telomerase reverse transcriptase
WHO	World Health Organization

Introduction

The 2016 World Health Organization (WHO) classification of tumors of the central nervous system (CNS) constituted a landmark in neuro-oncology, as it represented the first time CNS tumors were classified according to molecular features in addition to histological characteristics [1]. Although grouping tumors by similarities on histopathology has long been the standard for CNS tumor classification, this method has high intraobserver and interobserver variability, and results in inconsistent predictions of clinical outcomes [2, 3]. Improvements in our understanding of the genetic basis of tumorigenesis over the past two decades, and their implications on the clinical outcomes and prognosis of these patients, led to the integration of molecular features into CNS tumor classification. Several studies examining the distinct genetic alterations and clinical behavior of IDH-mutant and IDH-wildtype diffuse astrocytic gliomas resulted in the classification of these two entities into distinct groups in the 2016 WHO update [4, 5]. Previous studies have shown that a subset of IDH-wildtype diffuse or anaplastic astrocytomas in adults with radiographic and histologic features of WHO grade II or III tumors (absence of microvascular proliferation or necrosis), behave clinically aggressively with overall survival similar IDH-wildtype glioblastoma (GBM), WHO grade IV [4–6]. Conversely, other IDH-wildtype astrocytomas have better overall survival than GBM, but generally worse than IDH-mutant tumors. Therefore, the presence or absence of IDH mutation alone is insufficient to predict the clinical behavior of WHO grade II or III astrocytic tumors.

Due to the continuous rapid advancement of our understanding of the molecular mechanisms underlying brain tumor pathogenesis, cIMPACT-NOW (the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) was established in 2016 to provide updates in between official editions of the WHO classification of CNS tumors [7, 8]. In the cIMPACT-NOW update 3 report, the working committee concluded that histologic grade II and III IDH-wildtype diffuse astrocytic gliomas containing (i) telomerase reverse transcriptase (*TERT*) promoter mutations, and/or (ii) the combination of whole chromosome 7 gain and whole chromosome 10 loss (+7/−10), and/or (iii) epidermal growth factor receptor (*EGFR*) amplification, correspond to a WHO grade IV diagnosis and should be classified as *Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV* [9]. While the diagnostic molecular criteria of this entity have been examined in several studies [10–13], the literature evaluating the clinical and radiographic characteristics of these patients remains limited. In this study, we present a single-institution retrospective case series of 6 patients who were diagnosed with *diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV* (DAG-G), with confirmation by next-generation tumor sequencing. This single-institution series of DAG-G patients aims to detail their clinical, radiographic, and molecular findings, and examines the characteristic features distinguishing them from classic IDH-mutant astrocytomas, through a direct comparison with 7 patients diagnosed with WHO grade II or III IDH-mutant astrocytoma at our institution during the same time period.

Methods

Patient cases

Patient data was retrospectively extracted from the electronic medical record (EMR) for all patients undergoing surgical biopsy or resection of a WHO grade II or III astrocytoma at our institution from 2018 to 2020. From this database, we identified 6 patients with next-generation sequencing confirmed diagnosis of DAG-G on their surgical pathology reports. For each patient, we extracted data from their chart on patient demographics, imaging findings, surgical treatment, adjuvant chemotherapy and radiation treatment, complete histopathology, and clinical outcomes. Brain magnetic resonance imaging (MRI) for several patients was reported to be consistent with gliomatosis cerebri. The radiographic diagnosis of gliomatosis cerebri was defined as a confluent hyperintense T2-weighted MRI or T2-weighted fluid attenuation inversion recovery (FLAIR) imaging abnormality in at least 3 separate brain lobes. Molecular alterations recorded included mutations defining the cIMPACT-NOW update 3 criteria for diagnosis of DAG-G, such as *TERT* promoter mutations, +7/−10 chromosome, and *EGFR* amplification. Other molecular alterations recorded when available included *PTEN* deletion, *ATRX* loss, *MGMT* methylation,

p53 loss, *BRAF V600E*, and *CDKN2A/B* mutations. All patients were confirmed to lack *IDH-1* mutation, *IDH-2* mutation, or *1p/19q* co-deletion. Overall survival (OS) was calculated from the date of initial MRI to the date of death or last provider note in the EMR confirming the patient was still alive. Progression-free survival (PFS) was calculated from the date of surgery to the date of first imaging showing unequivocal tumor progression or last provider note. Follow-up was calculated from the date of surgery to the date of last provider note.

From the same patient database, we extracted similar data points for 7 patients with molecularly confirmed IDH-mutant WHO grade II or III astrocytoma as a comparison group. This study was approved by the University of California, Davis Institutional Review Board (IRB #1567550).

Literature search

We performed a PubMed literature search using a combination of the key words "IDH wildtype", "astrocytoma", "diffuse astrocytic glioma", "low grade", "c-IMPACT NOW", "TERT", "EGFR" and "glioblastoma". Studies published prior to 2015 or originally written in a non-English language were excluded. We elected not to include studies prior to 2015 in our search due to the publications of the WHO CNS tumor classification in 2016 and the c-IMPACT NOW update 3 criteria in 2018. The citations and their references were further individually reviewed for other relevant articles.

Statistical analysis

Statistical analysis was performed on GraphPad Prism 8 (GraphPad). Overall survival was estimated via Kaplan-Meier analysis, with differences in survival determined by log-rank test. Categorical variables were compared using Fisher's exact test. Continuous numerical variables were compared using two-sided unpaired Student's t test. Statistical significance was accepted for $p < 0.05$.

Results

Six patients with DAG-G were identified in our single-institution cohort. Patient demographics and clinical presentation are detailed in Table 1. The mean age at diagnosis was 67.7 years, with a standard deviation of 8.9 years. Three of the patients were male and 3 were female. Three patients exhibited varying levels of confusion, memory disturbance, or altered mental status at their initial presentation. Patient 2 subsequently deteriorated into a comatose state. The three patients who did not present with mental status changes presented instead with focal neurological deficits, including extremity weakness, numbness, and facial paresthesia.

Table 1 Clinical and radiographic characteristics of *Diffuse astrocytic glioma, IDH-WT, with molecular features of glioblastoma, WHO grade IV*

Case	Sex	Age (yrs)	Clinical Presentation	Radiology: Pattern	Radiology: Enhancement	Tumor Location	Hemisphere	Surgical Procedure (location)
1	M	83	Confusion/AMS	Multifocal	Yes (minimal)	Parietal, corpus callosum	Left	Biopsy (corpus callosum)
2	M	61	Syncope → AMS into coma	Gliomatosis cerebri/diffuse	Yes (moderate)	Temporal, occipital, corpus callosum, basal ganglia, thalamus, brainstem, cerebellum	Bilateral	Biopsy (left brachium pontis)
3	F	67	Intermittent LUE/LLE numbness, paresthesias, and mild weakness	Gliomatosis cerebri/diffuse	No	Frontal, parietal, corpus callosum, thalamus	Right	STR (75%)
4	F	69	Right facial paresthesias	Gliomatosis cerebri/diffuse	Yes (minimal)	Frontal, temporal, parietal, occipital, insula, corpus callosum, basal ganglia	Bilateral	Biopsy (right inferior frontal lobe)
5	M	57	6 months intermittent cognitive difficulty, memory loss, HA	Gliomatosis cerebri/diffuse	No	Frontal, temporal, parietal, corpus callosum, thalamus, brainstem	Bilateral	Biopsy (right temporooccipital lobe)
6	F	69	Numbness/tingling, right sided weakness, focal seizures → status epilepticus	Multifocal	Yes (minimal)	Frontal, corpus callosum	Bilateral	Open biopsy (left posterior frontal lobe)

AMS Altered Mental Status, *LUE* Left Upper Extremity, *LLE* Left Lower Extremity, *HA* Headache, *STR* Sub-Total Resection

Patient 6 was the only patient who presented to our institution with seizure activity. She presented with focal seizures which evolved into status epilepticus.

Imaging characteristics of our patients are detailed in Table 1. All patients had diffuse disease, with 4 patients meeting radiographic criteria for diagnosis of gliomatosis cerebri, and 2 with multifocal disease. All tumors were expansile, T2 hyperintense lesions with no or minimal enhancement. Involvement of both cerebral hemispheres was found in 4 patients, and unilateral lesions were found in two. All 6 patients presented with corpus callosum involvement.

All patients underwent a biopsy or surgical resection of their tumor. Stereotactic biopsy was performed in 4 patients, and open biopsy was performed in one. One patient underwent a sub-total resection (STR) resulting in 75% of the tumor debulked (patient 3).

Five patients had NGS data detailing expression of the high-grade molecular features of GBM as defined by the cIMPACT-NOW update 3 criteria (Supplementary Table 1). *TERT* promoter mutation was found in 4 patients, gain of whole chromosome 7 and loss of whole chromosome 10 in 3 patients (loss of whole chromosome 10 only in 1 patient), and *EGFR* amplification in 1 patient. None of the patients were found to have *ATRX* loss.

We compared the clinical, radiographic, and molecular characteristics of the 6 patients with DAG-G with 7 patients diagnosed with IDH-mutant low-grade or anaplastic astrocytoma (Table 2). The molecular features and histologic grade of these 7 IDH-mutant tumors are detailed in Supplementary Table 2. Compared to patients with IDH-mutant astrocytomas, mean age for patients with DAG-G was older (68 years vs 33 years, $p < 0.0001$) and median overall survival was significantly shorter (2.75 months vs median not reached, $p = 0.03$). DAG-G tumors were more diffuse (67 vs 0% with gliomatosis cerebri, $p = 0.02$) and more likely to present in both hemispheres (67 vs 0%, $p = 0.02$). IDH-mutant astrocytomas were more likely to present as a focal lesion (100 vs 0%, $p = 0.0006$). DAG-G tumors were more likely to present with corpus callosum involvement (100 vs 0%, $p = 0.0006$), and deep structure involvement - basal ganglia and thalamus (67 vs 0%, $p = 0.02$). Compared to IDH-mutant astrocytoma patients, DAG-G patients were more likely to undergo biopsy only (83 vs 0%, $p = 0.005$), and less likely to undergo gross-total resection (GTR) of their tumor (0 vs 71%, $p = 0.02$). We also found DAG-G patients presented less often with seizures ($p = 0.10$), and more often with focal neurological deficits with a lower KPS ($p = 0.006$).

Data on patients with IDH-wildtype grade II or III astrocytomas from 12 studies published in the literature between 2015 and 2019 were extracted and compiled as shown in Table 3 [4, 5, 10–19]. The average age of the subjects in the studies ranged from 46 to 69 years. A subset of these patients from each study was reported as expressing *TERT* promoter mutations, *EGFR* amplification, and/or various combinations of whole or partial +7/−10 chromosome alterations. Median OS reported across these studies ranged from 9 months to 30 months, with the majority falling between 15 to 25 months. Importantly, many of these studies included tumors with oligoastrocytoma histology, and some with oligodendroglioma histology, in their cohorts.

Discussion

In this study, we presented a single-institution retrospective series of 6 patients who were diagnosed with *diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV* (DAG-G) and detailed their clinical presentation, radiographic characteristics, molecular alterations, and treatment. DAG-G represents a new entity proposed by the cIMPACT-NOW committee to re-classify a subset of IDH-wildtype diffuse or anaplastic astrocytomas into a WHO grade IV category. These tumors, which typically exhibit features on radiology and histopathology that would otherwise classify them as WHO grade II or III tumors, present with an aggressive clinical course and overall survival more similar to patients with IDH-wildtype glioblastoma, WHO grade IV [10–13, 19]. To date, there have been limited data available on the radiographic and clinical presenting characteristics of this relatively new entity, particularly in comparison to traditional IDH-mutant astrocytomas [20].

On the basis of imaging and histopathology alone, DAG-G can be quite difficult to distinguish from traditional IDH-mutant low grade astrocytomas. Although the DAG-G tumors in our cohort were generally more widespread than our comparison group of IDH-mutant astrocytomas, both appeared as non- or minimally-enhancing T2 hyperintense lesions (Fig. 1). Additionally, the DAG-G tumors had histopathology with classic features of a low-grade glioma (Fig. 2). Molecular studies were necessary to clearly diagnose DAG-G.

We found the majority of our DAG-G patients presented with altered mental status or focal neurological deficits, while only 1 patient presented with seizures, which is contrary to other studies in the literature reporting 48–65% of their DAG-G patients presenting with seizures [14, 18]. When compared to our cohort of patients with IDH-mutant astrocytomas, we noted a trend towards significance ($p = 0.10$) for decreased frequency of seizures on initial presentation in DAG-G patients compared with IDH-mutant astrocytomas. Large, rapidly growing, high-grade gliomas have been reported to present more frequently with non-seizure neurological symptoms, as seizures are more often associated with smoldering glial changes seen in low-grade

Table 2 Comparison of clinical, radiographic, and molecular characteristics of *Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma* vs. IDH-mutant WHO grade II/III astrocytoma

Characteristics	Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV	IDH-mutant astrocytomas, WHO grade II/III	*p* value
Patients, *n*	6	7	
Age (years)			< 0.0001
Mean	67.7	33.1	
Median	68	30	
Range	57–83	25–47	
Overall Survival (months)			0.03
Median	2.75	Not reached	
Range	1.25–4.75	N/A	
Follow Up (months)			
Median	1	17.3	
Range	0.5–1.5	1.25–66.3	
Clinical Presentation, *n* (%)			
Confusion/AMS	3 (50)	2 (29)	0.59
Seizures	1 (17)	5 (71)	0.10
Weakness	2 (33)	0 (0)	0.19
Sensory	3 (50)	0 (0)	0.07
HA	1 (17)	2 (29)	> 0.99
Syncope	1 (17)	0 (0)	0.46
Gait Ataxia	0 (0)	1 (14)	> 0.99
Incidental	0 (0)	1 (14)	> 0.99
Surgical Procedure, *n* (%)			
GTR	0 (0)	5 (71)	
STR	1 (17)	2 (29)	
Biopsy	5 (83)	0 (0)	0.005
Adjuvant Therapy, *n* (%)			
Chemoradiation	0 (0)	3 (43)	0.19
Hemisphere, *n* (%)			
Right	1 (17)	4 (57)	0.27
Left	1 (17)	3 (43)	0.56
Bilateral	4 (67)	0 (0)	0.02
Tumor Location, *n* (%)			
Frontal Lobe	4 (67)	4 (57)	> 0.99
Temporal Lobe	3 (50)	4 (57)	> 0.99
Parietal Lobe	4 (67)	1 (14)	0.10
Occipital Lobe	2 (33)	0 (0)	0.19
Insula	1 (17)	2 (29)	> 0.99
Corpus Callosum	6 (100)	0 (0)	0.0006
Basal Ganglia	2 (33)	0 (0)	0.19
Thalamus	3 (50)	0 (0)	0.07
Brainstem	2 (33)	0 (0)	0.19
Deep Structures (basal ganglia, thalamus)	4 (67)	0 (0)	0.02
Cerebellum	1 (17)	0 (0)	0.46
Growth Pattern, *n* (%)			
Gliomatosis Cerebri	4 (67)	0 (0)	0.02
Multifocal	2 (33)	0 (0)	0.19
Focal	0 (0)	7 (100)	0.0006
Contrast Enhancement, *n* (%)			

Table 2 (continued)

Characteristics	Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV	IDH-mutant astrocytomas, WHO grade II/III	*p* value
Present	4 (67)	4 (57)	> 0.99
Not Present	2 (33)	3 (43)	> 0.99
Molecular Alteration, *n* (%)			
pTERT mutation	3 (60)	0 (0)	0.05
+7/−10 chromosome	3 (60)	0 (0)	0.05
EGFR amplification	1 (20)	0 (0)	0.42
pTERT or + 7/−10 or EGFR	5 (100)	0 (0)	0.001
p53 loss	4 (67)	7 (100)	0.19
ATRX loss	0 (0)	6 (86)	0.005
MGMT methylation	1 (17)	1 (14)	> 0.99

AMS Altered Mental Status, *HA* Headache, *GTR* Gross-Total Resection, *STR* Sub-Total Resection, *pTERT* Telomerase Reverse Transcriptase Promoter, *EGFR* Epidermal Growth Factor Receptor, *ATRX* Alpha-Thalassemia/Mental Retardation Syndrome X-Linked, *MGMT* O-6-Methylguanine-DNA Methyltransferase

tumors [21]. The diffuse, rapidly growing nature of DAG-G tumors may progress too quickly for seizure activity to develop, and instead present with symptoms related to mass effect, such as focal neurological deficits or altered mental status. Additionally, low-grade IDH-mutant astrocytomas have shown a propensity to develop in epileptogenic regions of the brain, such as the frontal and temporal lobes [22, 23], and prior studies have demonstrated that tumors located in superficial cortical areas are more likely to present with seizures [21, 24]. Our DAG-G cohort in this study was associated with predominantly deep-seated white matter lesions.

Tumor characteristics, treatment and outcomes

We found that DAG-G patients were significantly more likely to present in a diffuse pattern involving bilateral cerebral hemispheres compared to classic IDH-mutant astrocytomas. The term gliomatosis cerebri was removed from the 2016 WHO classification as a separate nosological category, and is now categorized as a growth pattern with widespread involvement [1]. In their study of 89 patients with tumors exhibiting gliomatosis cerebri growth patterns, Kwon et al. found 70% of their cohort had IDH-wildtype diffuse or anaplastic astrocytomas, 25% had IDH-mutant diffuse or anaplastic astrocytomas, and 5% had IDH-wildtype or IDH-mutant glioblastomas [25]. Multiple studies have demonstrated substantial subsets of IDH-wildtype astrocytomas expressing *TERT* promoter mutations, chromosome 7 gain/10 loss, or *EGFR* amplification, with one study reporting expression in over 50% of their cohort [4]. Therefore, in a patient presenting with radiographic imaging suggestive of a diffuse glioma growth pattern, the clinician must remain aware of the significant possibility of the lesion representing a DAG-G. As IDH-mutant astrocytomas with a more benign clinical course can also present similarly, imaging alone is insufficient for differentiation. A biopsy is necessary for confirmation of a DAG-G diagnosis.

Due to the diffuse nature of these tumors, 5 of our patients underwent biopsy only, and 1 received a STR. The infiltration of these tumors into deep structures such as the thalamus and basal ganglia, results in a surgical predicament whereby resection cannot be performed without risking devastating neurological consequences. While surgical intervention beyond a biopsy is often not possible, adjuvant therapies such as radiation therapy and chemotherapy can be utilized. In their series of 54 gliomatosis cerebri patients, Chen and colleagues found radiation therapy was associated with better progression-free and overall survival ($p < 0.01$), but chemotherapy was not [26]. The lack of efficacy of chemotherapy is likely due to the fact that most of these patients had IDH-wildtype tumors, most of which are also MGMT promoter unmethylated. In our DAG-G cohort, only 1/6 patients was positive for MGMT promoter methylation. As in patients with MGMT unmethylated, IDH-wildtype GBM, the benefit of alkylating chemotherapy is questionable. Only a subset of patients in other published DAG-G cohorts received adjuvant radiation therapy or chemoradiation (68% of patients in Tesileanu et al. and 70% in Wijnenga et al.) [14, 18] as part of their treatment. In our DAG-G cohort, no patients received additional radiation or chemotherapy treatment after diagnosis. All patients in our cohort presented with advanced disease and had profound neurologic deficits (including altered mentation or coma) at the time of biopsy. None of these patients demonstrated significant improvement in function with the initiation of steroids. Because their poor functional status and the overall poor prognosis of their disease, the patients and/or families in each case elected to transition to hospice rather than pursue life-prolonging therapy. The lack of treatment accounts for the limited median overall survival of only 2.75 months in

Table 3 Study characteristics from literature review

Citation	Year	Study type	Molecular stratification	n (IDH-WT grade II/III gliomas)	Age	Grade II vs. III (%)	Total mutations (%)	OS (months)
Tesileanu et al.	2019	R	*IDH1/2* status, +7/−10, p*TERT* mutation, *EGFR* amplification	71	58 (19–78)	II: 63 III: 20 NOS: 17	TERT: 94 +7/−10: 59 EGFR: 24	23.8
Kuwahara et al.	2019	CS	*IDH1/2* status, +7, −10q, p*TERT* mutation	35	59 (23–81)	II: 23 III: 77	TERT: 15 +7: 43 -10q: 14	Any combination of TERT, +7, and -10q: 18.5
Morshed et al.	2019	CS	*IDH1/2* status, p*TERT* mutation	7	68.7*	II: 100**	TERT: 67	All IDH-WT DA ($n=7$): 40.7, 95% CI: [14.1–67.4]
Christians et al.	2019	R	*IDH1/2* status, *EGFR* amplification	10	N/A	III: 50	EGFR: 50	9
Aoki et al.	2018	R	*IDH1/2* status, +7p/−10q, p*TERT* mutation	137	JPN: 50 [41–65] TCGA: 55 [45–62]	II: 26 III: 74	TERT: 29 +7p: 31 -10q: 24	JPN: 29.4, 95% CI: [25.2–49.3] TCGA: 21.4, 95% CI: [18.5–26.8]
Stichel et al.	2018	R	*IDH1/2* status, +7/−10, *EGFR* amplification	227	N/A	II: 19 III: 81	+7/−10: 43 EGFR: 34	N/A
Wijnenga et al.	2018	R	*IDH1/2* status, p*TERT* mutation, +7/−10q, *EGFR* amplification	23 (includes OD and OA histology)	61 [52–65]	II: 100	N/A	25.2
Wijnenga et al.	2017	R	*IDH1/2* status, +7/−10q, p*TERT* mutation	74	56 [47–63]	II: 72 III: 28	TERT: 70 +7/−10q: 53	TERT: 8–12 +7/−10q: 24–28
Aibaidula et al.	2017	R	*IDH1/2* status, p*TERT* mutation. *EGFR* amplification	142 (includes OD and OA histology)	46 (18–76)	II: 51 III: 49	TERT: 26 EGFR: 14	TERT: 15.8 EGFR: 12.4
Eckel-Passow et al.	2015	R	*IDH1/2* status, p*TERT* mutation	97	pTERT mutant: 59.5 (median)	II: 31 III: 69	TERT: 60	TERT: 20–24 No TERT: 36–40
Brat et al.	2015	R	*IDH1/2*status, +7/−10, p*TERT* mutation, *EGFR* amplification	55 (includes OD and OA histology	49.9 ± 15.3	II: 16 III: 84	TERT: 18 +7/−10: 58 EGFR: 46	20.4
Weller et al.	2015	P	*IDH1/2* status, +7q/−10q, p*TERT* mutation	21 (includes OA histology)	52 ± 11	II: 24 III: 76	TERT: 43 +7q/−10q: 62	TERT: 28.8

CS case series, *P* prospective study, *R* retrospective study, *DA* diffuse astrocytoma, *OD* oligodendroglioma, *OA* oligoastrocytoma

Data are presented as median (range), median [IQR], or mean ± SD

*All patients in this study were over 60, the listed value is an average

**All patients in this study had a WHO grade II glioma

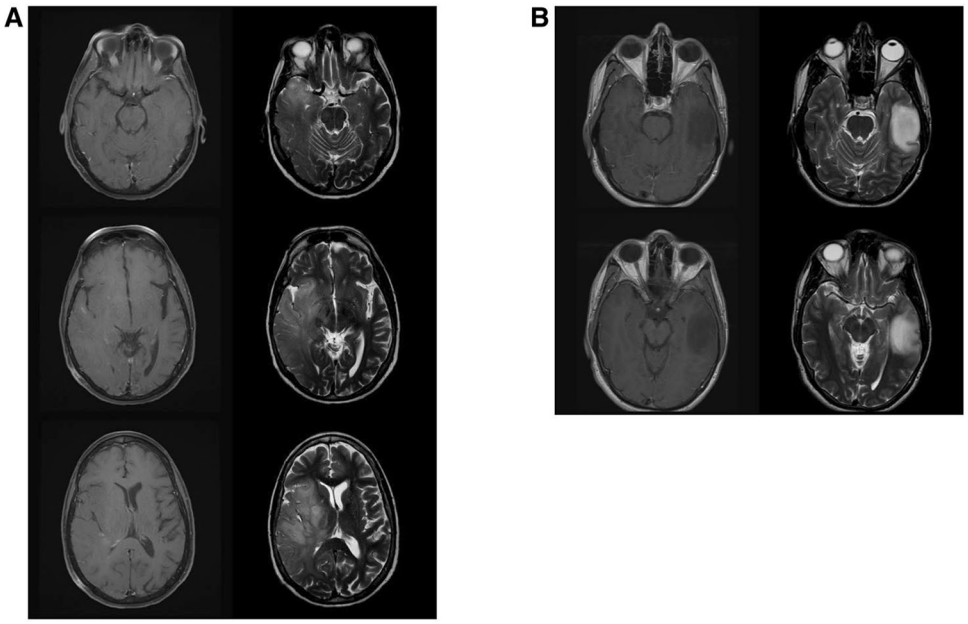

Fig. 1 Imaging features of patients with *Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV*. (**a**) Axial T1 with contrast and T2 imaging of a patient at our institution demonstrating non-enhancing diffuse pattern lesion involving the right temporal lobe, insula, basal ganglia, internal capsule, frontal lobe, and parietal lobe. The patient had contralateral frontal lobe involvement through infiltration of the corpus callosum. (**b**) Axial T1 with contrast and T2 imaging of a patient at our institution with IDH-mutant diffuse astrocytoma WHO grade II demonstrating a focal, non-enhancing mass of the left temporal lobe that is typical of low-grade gliomas

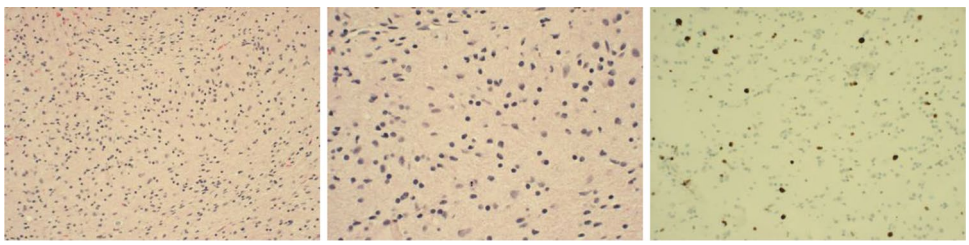

Fig. 2 Histopathology of patients with *Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV*. Hematoxylin and eosin stain of DAG-G tumor at 200x (left) and 400x (center) demonstrating features typical of WHO grade II low-grade astrocytomas, including moderate cellularity, mild nuclear atypia, and lack of mitosis, microvascular proliferation, or necrosis. Ki-67 stain (right) demonstrated low proliferation <5% Ki-67 index

our patients. As other studies of DAG-G report frequencies of only 30–36% of patients with a gliomatosis cerebri-like pattern of tumor infiltration [14, 18], our high rate of diffuse tumor at presentation (67%) also contributed to the particularly poor survival of our cohort.

Recommendations and limitations

Compared to our IDH-mutant astrocytoma patients, our cohort of 6 DAG-G patients presented at an older age and had significantly more impaired neurologic function at presentation, accounting for a shorter median overall survival of only 2.75 months. Due to the unresectable nature of many of these tumors, combined with the high-grade molecular features and aggressive clinical course mirroring that of IDH-wildtype glioblastoma WHO grade IV, we recommend prompt surgical biopsy (or resection when possible) for these patients for confirmation of the diagnosis, and immediate initiation of adjuvant radiation and/or chemotherapy. The molecular studies necessary to confirm the diagnosis of DAG-G can take up to 2–3 weeks to return, especially when sequencing is not available in-house. As these patients can have rapid disease progression with neurologic deterioration, we recommend initiating treatment planning early on the basis of clinical characteristics suggesting DAG-G with histopathology demonstrating diffuse astrocytoma. That way, treatment can begin immediately, once the molecular diagnosis is confirmed. While larger cohorts of DAG-G patients are needed to confirm the frequency of the clinical and radiographic presentation we observed in our patients, one should be aware of the possibility of this diagnosis in an elderly patient who presents with symptoms of mass effect and imaging features of a low-grade diffuse glioma that is minimally enhancing, involves both hemispheres and deep brain nuclei. Future prospective studies will be necessary to evaluate the true benefits of chemoradiation in this patient population.

The rarity of this newly established diagnosis and our single-institution cohorts resulted in a small sample size and difficulty achieving statistical power in our comparison to IDH-mutant WHO grade II/III astrocytomas. Furthermore, published studies on DAG-G in the literature are sparse, and primarily consist of retrospective studies of non-disaggregated patient data comprising multiple histology types, and with a focus on molecular alterations and survival. We acknowledge that our study would be better served with a comparison of DAG-G patients to IDH-wildtype WHO grade II/III patients lacking the cIMPACT-NOW update 3 molecular markers of GBM, and recognize this as a shortcoming of our study. However, given that IDH-wildtype astrocytomas lacking the molecular features of DAG-G are even more rare than DAG-G, we were unable to identify any patients from our institution that would meet the criteria for this diagnosis. Furthermore, a comparison to IDH-wildtype WHO grade II/III patients in the literature is challenging due to the lack of published studies with disaggregated patient data separating DAG-G from other IDH-wildtype astrocytomas.In their cohort of 16 patients with IDH-wildtype grade II or III astrocytomas, Tesileanu et al. reported a median age of 45 years, gliomatosis pattern on imaging in 19% of their cohort, and a significantly longer median OS (median not reached, $p < 0.001$) compared to DAG-G [14]. To our best knowledge, this is the largest published cohort of IDH-wildtype grade II or III astrocytomas lacking cIMPACT-NOW update 3 molecular markers currently available in the literature. As discussed, their median age was significantly lower than the patients in our study, with far fewer patients presenting with a diffusely infiltrative pattern of disease. Therefore, in older patients presenting with diffuse disease, the diagnosis of DAG-G should be considered early even when radiographic features and initial histopathology point to a low-grade tumor. We recommend starting adjuvant chemoradiotherapy early in patients with sufficiently high clinical suspicion for DAG-G, rather than awaiting final molecular analysis, which can delay care by several weeks.

Conclusion

Patients with *Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV* are more likely to be older than typical IDH-mutant WHO grade II/III astrocytoma patients, with more diffuse tumors and present with focal neurological deficits. When such patients are encountered, prompt biopsy/resection for confirmation of the diagnosis and immediate initiation of adjuvant therapy is recommended, as the disease progression and overall prognosis is similar to glioblastoma.

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Data availability Data and material available by request

Code availability Not applicable

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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