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Case Report

IDH1-mutant primary intraventricular gliosarcoma: Case report and systematic review of a rare location and molecular profile

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ABSTRACT

Background: Gliosarcoma (GS) is classified as an IDH-wild-type variant of glioblastoma (GBM). While GS is already an unusual presentation of GBM, IDH1-mutant cases are especially rare. We present an IDH1-mutant primary intraventricular GS case report and a systematic review of the molecular profile in GS correlating to the prognostic and pathogenesis of IDH1/2 mutations.

Case Description: A 44-years-old man presented with ongoing fatigue symptoms and a new-onset intense occipital headache. The patient complained of memory loss, dyscalculia, and concentration difficulties. An MRI revealed a bihemispheric intraventricular mass crossing the midline through the corpus callosum and infiltrating the trigone of the lateral ventricles, hypointense, and hyperintense on the T1- and T2-weighted image. We performed a microsurgical resection with a transparietal transsulcal approach; however, the contralateral mass was attached to vascular structures and we decided to reoperate the patient in another moment. The histopathological study showed a Grade IV tumor and the immunohistochemistry confirmed the diagnosis of GS. The patient presented progressive neurologic decline and died 45 days after the surgical approach.

Conclusion: We did two systematic reviews studies from PubMed, EMBASE, MEDLINE, Cochrane, and SCOPUS databases, and included molecular and intraventricular studies of GS. We performed further meta-analysis using OpenMetaAnalyst™ software. We conducted a forest plot with the molecular profile of GS. When correlated IDH1 mutation versus tp53 mutation, we found an odds ratio (OR) of 0.018 (0.005–0.064) and $P < 0.001$. Moreover, we compared IDH1 mutation versus MGMT methylation ($P = 0.006$; OR = 0.138 [0.034–0.562]). The studies evaluating the molecular profile in GS prognostics are often extended from all GBMs despite specifics GBM variants (i.e., GS). We found a correlation between IDH1 mutation expression with tp53 and MGMT expression in GS, and future studies exploring this molecular profile in GS are strongly encouraged.

Keywords: Case report, Cerebral ventricle neoplasms, Gliosarcoma, Human IDH1 protein, Systematic review

INTRODUCTION

Gliosarcomas (GS) are rare primary high-grade brain tumors and a variant of GBM, constituting 2-8% of all GBM.[15,16,20-24,26,29,45-48] They are classified as IDH-wildtype variant[2,29] with two different components: gliomatous part (i.e., astrocytic with areas of necrosis, and fulfilling the criteria

for glioblastoma [GBM]) determined by the identification of GFAP; and a sarcomatous part that resemble a spindle cell sarcoma determined by the presence of the reticulin element.[15,16,31,24,45,46,48] The exact pathogenesis is unknown, one theory suggests that sarcomatous components originated from the malignant transformation of hyperplastic blood vessels.[15,16,24,31,45,46,48]

A modest propensity for temporal lobe involvement was observed in GS followed by the frontal, parietal, and occipital lobes. Cerebellum, pineal region, cerebellopontine angle, intraventricular, and spinal cord have been described as rare primary locations for these lesions.[16,21,24,26,39,43,45,46,48]

Headache was the most common presentation of intraventricular GS, other clinical symptoms including aphasia hemiparesis, seizures, and cognitive decline depends on location, size of the tumor, and the existence of hydrocephalus.[16,21,42,48] The age of onset is usually between 40 and 70 years and is more frequent in men than in women. GS has a poor prognosis and a median OS rate varying from 4 to 17.5 months.[8,16,17,26]

We present a rare case of an IDH1-mutant primary intraventricular GS and a systematic review of the molecular profile in GS correlating to the prognostic and pathogenesis of IDH1/2 mutations.

CASE REPORT

Patient

A 44-years-old man presented with ongoing fatigue symptoms and a new-onset intense occipital headache which was worse in the night and was waking him up from sleep. The patient reported progressive deterioration of the symptoms with increased intensity and frequency of the headaches; moreover, he complained of memory loss, dyscalculia, concentration difficulties, psychomotor agitation, and aggressive behavior.

He was initially treated with dipyrone (4 g/day, oral), naproxen sodium (550 mg/day, oral), and dexamethasone (24 mg/day, oral) from urgent care, and referred to the neurosurgery department. He presented a normal mental status (GCS 15) without impairment on his physical examination and mild bilateral papilledema on his neurological examination.

Imaging

It was performed a brain MRI [Figure 1a-f] that revealed a hypointense bihemispheric intraventricular mass on the T1-weighted image and hyperintense mass on the T2-weighted image, crossing the midline through the corpus callosum and infiltrating the trigone of the lateral ventricles. The brain MRI also revealed a heterogeneous contrast enhancement with an important cystic component. The volume of the lesion (manual segmentation) was 63.1 cc and the estimated mean diameter was 50.15 mm. The initial hypothesis was GBM or anaplastic ependymoma. We discussed with the patient about the option of stereotactic biopsy to obtain samples for diagnostic purposes. However, the patient opted for microsurgery for maximum resection of the lesion; however, the gross-total resection was not achievable due to tumor extension.

Surgery

We decided to perform a microsurgical resection with a right transparietal transsulcal approach, reaching the trigone of the right ventricle and the infiltrative mass. We resected the ipsilateral brain lesion; however, the contralateral ventricle resection was limited due to a deep surgical corridor and the need to manipulate vascular structures (i.e., vein of Galen). The immediate postoperative MRI revealed a residual tumor volume of 14.03 cc (estimated mean diameter of 30.58 mm) in the left ventricular trigone [Figure 2a-f]. The histopathological study [Figure 3a-d] showed a GS - Grade IV tumor and the immunohistochemistry [Figure 4a-i] confirmed the diagnosis of GS (WHO - 2016).

Postoperative evaluation

After 20 days of the procedure, the patient presented an improvement of headache and psychomotor agitation; however, he continued with progressive worsening of memory loss and showed a diminished spatial awareness.

We started adjuvant radiotherapy and chemotherapy with temozolomide. However, one month after the tumor resection, a new MRI revealed important residual lesion growing on the trigone of the left ventricle with a tumor volume of 41.6 cc (estimated mean diameter of 43.65 mm) and an impressive growth rate estimated in 176.68 mm/year [Figure 5a-c]. The patient had a progressive neurologic decline and died 45 days after the surgical approach.

MATERIALS AND METHODS

We performed two systematic reviews of the literature using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and protocol. A literature search was performed using PubMed, EMBASE, Ovid MEDLINE, Cochrane Library, and SCOPUS databases. Search terms included (GS) AND [(idh1) OR (idh2) OR (atrx) OR (p53) OR (tert) OR (1p19q) OR (Ki-67)] in our first systematic review [Figure 6], and (GS) AND (intraventricular) in our second systematic review [Figure 7]. We selected full-text articles published from January 1990 to February 2020. Screening of titles and abstracts was performed, and further evaluation of full-text publications was used to select studies.

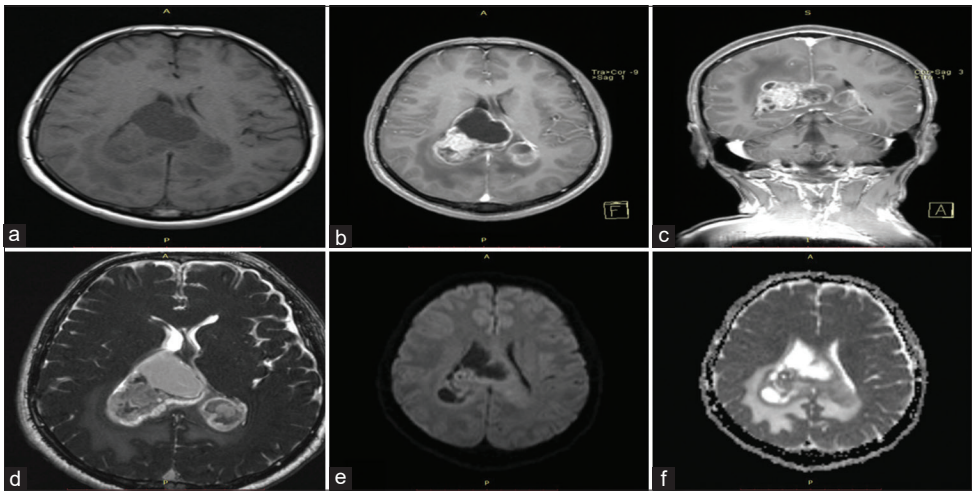

Figure 1: Preoperative MRI dated 1 month before surgery. (a) Axial T1WI MRI showing extensive amorphic heterogeneous mass invading both lateral ventricles with a commitment of midline. (b) Axial T1WI Gd MRI demonstrates the same lesion with ring and internal enhancement. (c) Coronal T1WI Gd MRI showing better the internal enhancement and commitment of both lateral ventricles. (d) Axial T2WI MRI exhibiting heterogeneous intratumoral signal and irregular-margin enhancement. Note hypointense signal surrounding the lesion suggesting extensive vasogenic edema. (e) Axial DWI shows nonimpaired diffusion. (f) ADC Map demonstrating high signal.

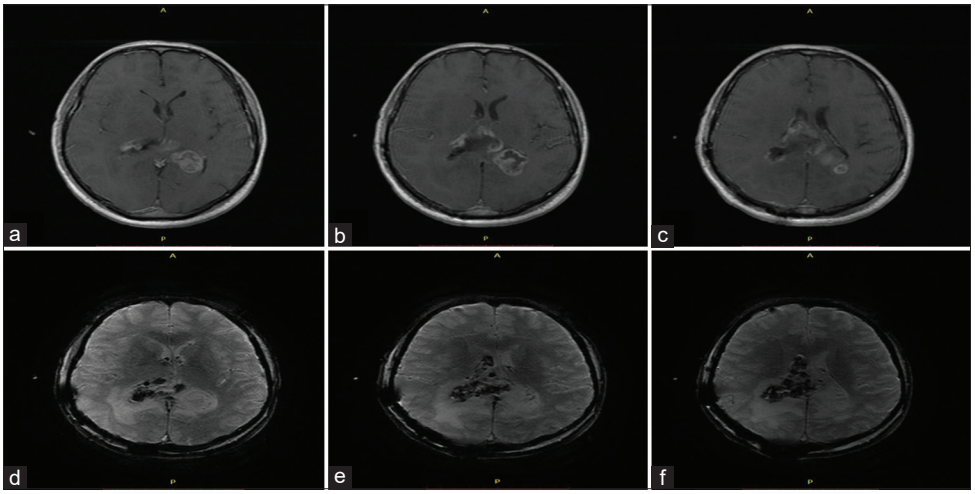

Figure 2: Immediate postoperative Control MRI. (a-c) T1WI Gd MRI exhibiting residual mass on the left ventricle atrium. (d-f) T2WI MRI demonstrating residual mass on the left ventricle atrium.

The inclusion criteria in our first systematic review were case series studies with at least ten patients containing GS with molecular profile study (IDH1/2, ATRX, tp53, TERT, 1p19q, or Ki-67). Cases series without any molecular profile were excluded from the study.

In our second review, we included only case series studies containing primary GS in the intraventricular location, the exclusion criteria were case series without exclusive GS intraventricular location.

Included studies were assessed by two authors (L. J. M. M. F and L. A. F. A.) to ensure that cases were correctly included in the study. Patient data from multiple studies were combined into two tables for comparison [Tables 1 and 2].

We used the maximal tumor diameter as a parameter of a possible outcome. In this case, we transformed the tumor volume (V) in an equivalent mean tumor diameter (MTD) using the formula [MTD = (2 × V)1/3] to standardize our study.[38]

The OpenMetaAnalyst™ meta-analysis software (Brown University, RI, USA) was used to perform a forest plot correlating IDH1 versus tp53 and IDH1 versus MGMT methylations in the case series of [Table 1].[1,5,6,18,19,28,32,37,40,41] The results were expressed as mean ± SD. The differences were considered statistically significant when $P < 0.05$.

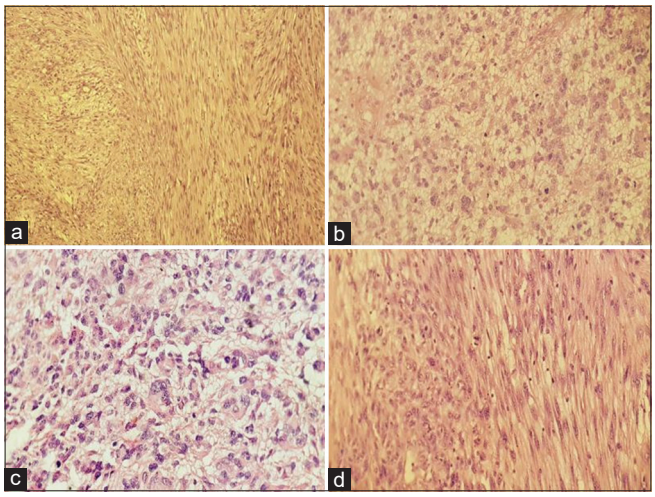

Figure 3: (a) Sarcomatous component, with marked pleomorphic spindle cells and mitotic activity (H and E, ×10). (b) Glial component, presenting hypercellularity, pleomorphism, mitotic figures, and nuclear atypia (H and E, ×20). (c) Glial component. Featuring hypercellularity, a high degree of anaplasia, presence of bizarre multinucleated cells, nuclear atypia, and evident mitotic figures (H and E, ×40). (d) Sarcomatous component, presenting mitotic figures, and nuclear atypia (H and E, ×20).

RESULTS

A total of 8 series were included in our first systematic review focused mainly on GS molecular signature. A total of 192 patients were identified [Table 1], most of them were male (64.06%). The mean diameter size was 4.87 (±0.91) cm. Only five case series (132 patients) had reported the tumor location: the temporal lobe was the most common location (39.46%), followed by frontal lobe (29.93%), parietal lobe (14.29%), occipital lobe (6.80%), other locations – nonspecified (4.08%), corpus callosum (2.72%), cerebellum (1.36%), cingulate gyrus (0.68%), and brainstem (0.68%).

Regarding the GS molecular profile studies found in the collected articles, we identified IDH1 mutations in 5.88% (n = 4/68) and TP53 mutations in 57% (n = 57/100) of patients. TERT mutations and 1p/19q codeletion were reported, respectively, in 70.3% (n = 26/37) and 35.3% (n = 6/17) of patients. Ki-67 index ≥23% was measured in 46.15% (n = 12/26) of evaluated patients. Methylated MGMT was identified in 22.68% (n = 22/97) of the patients. The mean OS of these patients was 12.51 (± 3.02) months and the median was 12.3 months.

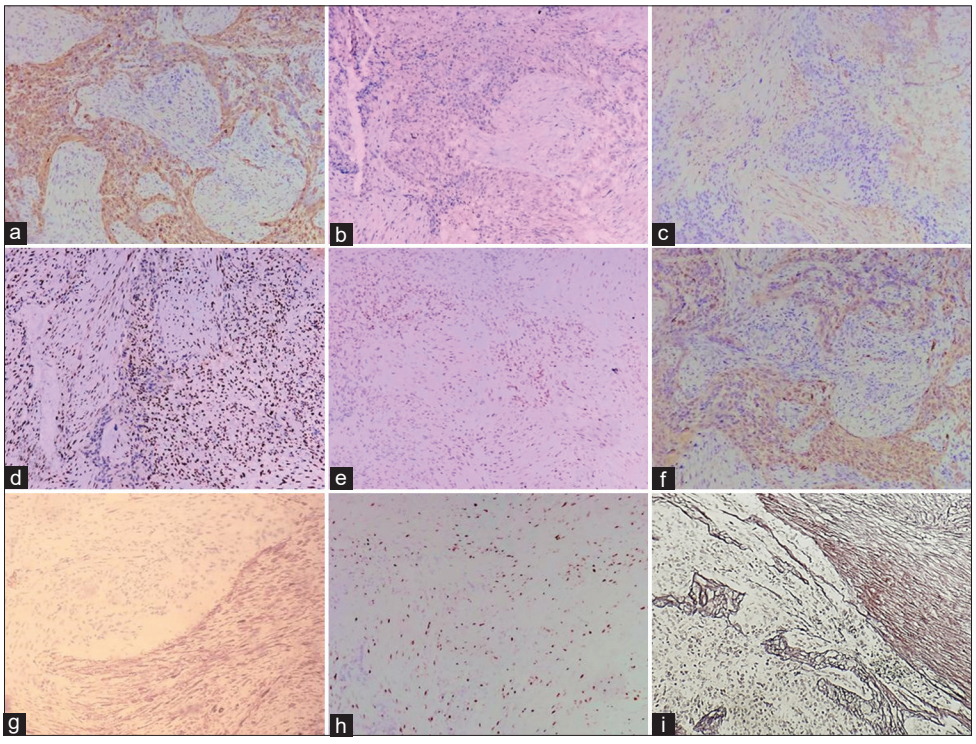

Figure 4: Immunohistochemical stains. (a) Focal positivity for GFAP, only in glial component (×10). (b) IDH was positive in the glial component (×10). (c) SMA (Smooth Muscle Actin) was positive in the sarcomatous component (×10). (d) Partial loss of ATRX expression (intact) in tumor cells (×10). (e) S100 was positive in the glial component (×10). (f) Vimentin was positive in the sarcomatous component (×20). (g) Diffuse positivity for p53 stain - approximately 80% of neoplastic cells (×10). (h) Ki-67 stain showed more than 60% proliferative activity in the tumor nuclei - 35% of neoplastic cells (×10). (i) Gomori silver stain highlights reticulin, negative in the glial component, and positive in the sarcomatous component.

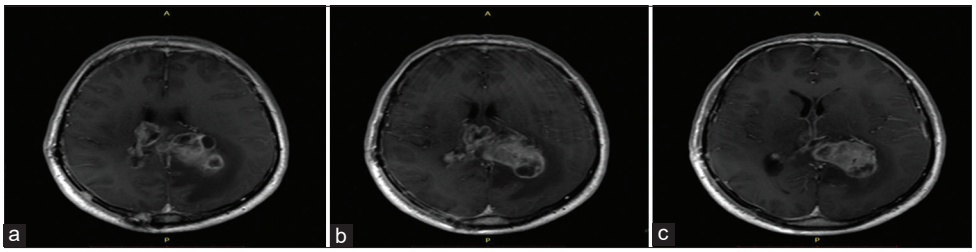

Figure 5: Postoperative MRI one month after surgery. (a-c) Axial T1WI Gd MRI showing notorious residual lesion growth.

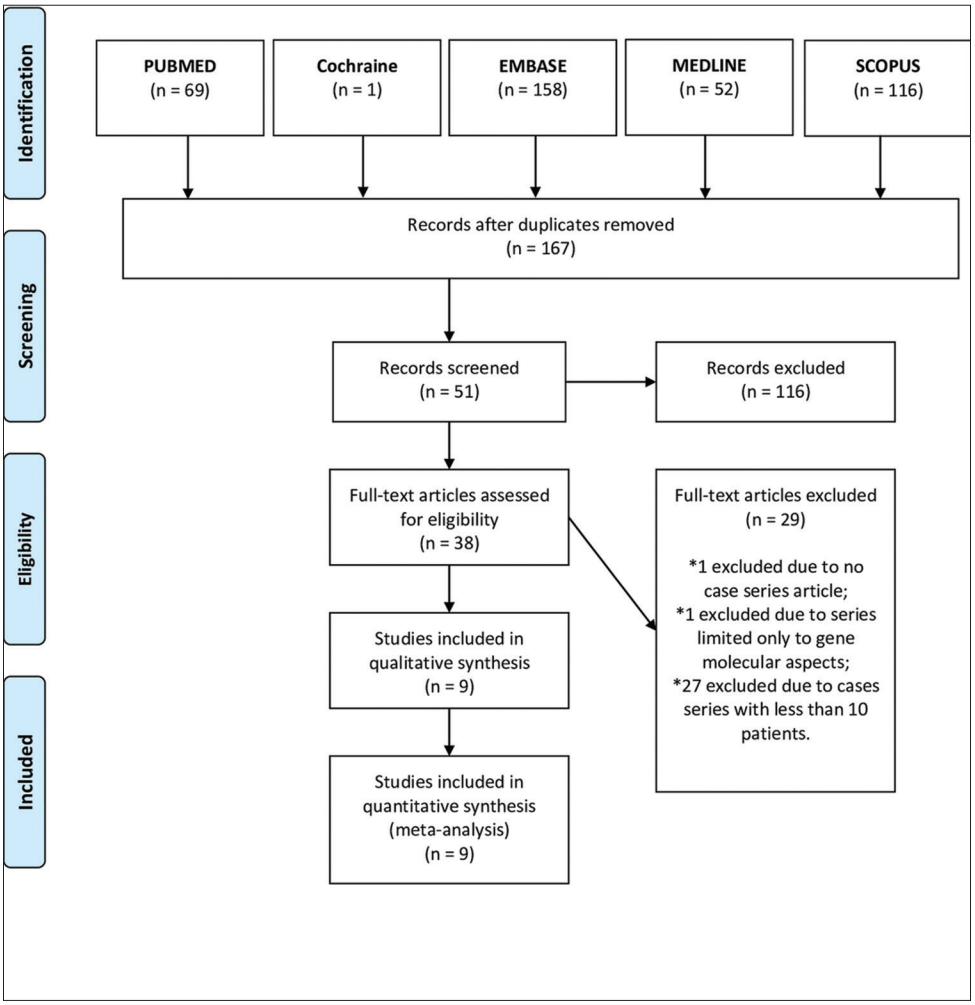

Figure 6: PRISMA 2009 flow diagram – Gliosarcoma molecular profile study.

We conducted a forest plot with the molecular profile of GS [Figure 8]; crossing IDH1 mutation versus tp53 mutation we found an estimated odds ratio of 0.018 (0.005–0.064) and $P < 0.001$. Moreover, we compared IDH1 mutation versus MGMT methylation and found a $P = 0.006$ and an odds ratio of 0.138 (0.034–0.562).

Our second systematic review included a total of ten intraventricular GS and we included our case for further evaluation [Table 2]. Out of 11 patients, seven were male (63.63%) and the mean diameter was 4.01 (±1.01) cm. The molecular profile study revealed tp53 mutations on four out of five patients (80%), IDH1 mutation was positive in only one patient (50%). ATRX was retained in two patients. Ki-67 index ≥ 23% was measured in 50% of patients. The mean OS of intraventricular GS was 4.75 (± 2.59) months and the median was 5 months. Transcortical approach was the most common neurosurgical technique in intraventricular GS (71.42%) and gross-total resection was achieved in only 50% of patients.

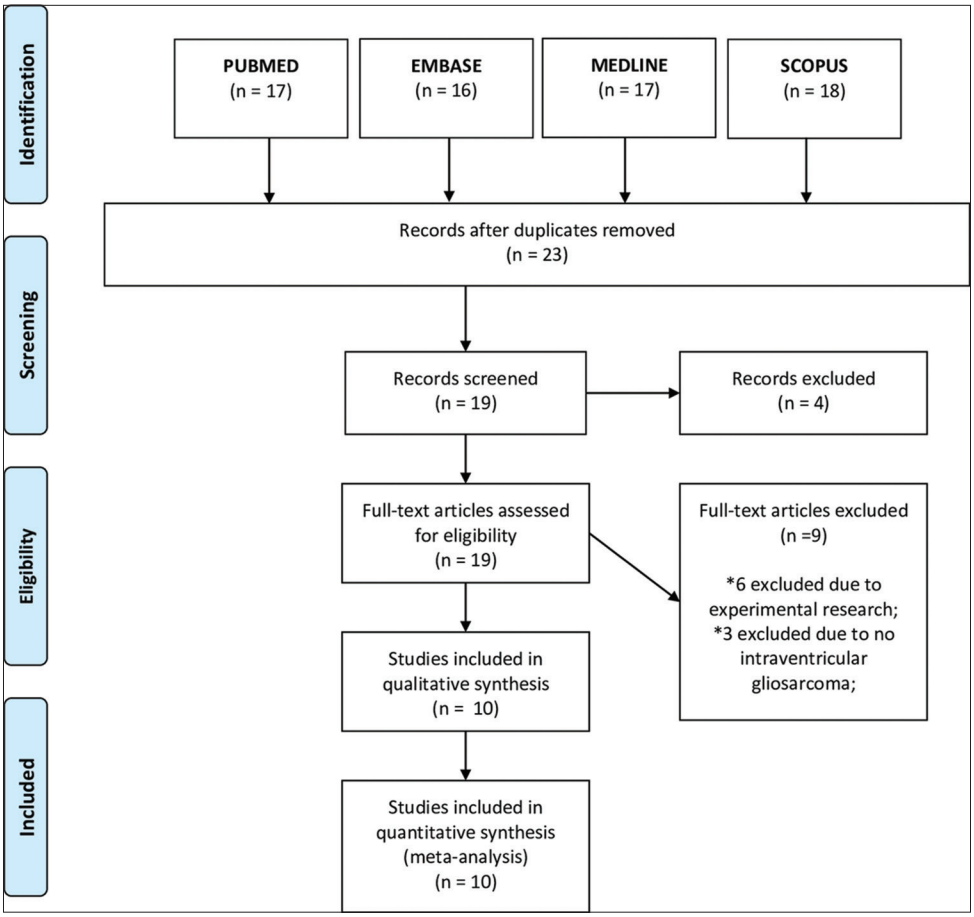

Figure 7: PRISMA 2009 flow diagram – Gliosarcoma intraventricular location.

DISCUSSION

IDH1/2 has an important role in chemo and/or radiotherapy in many types of tumors,[33] and this unique molecular signature (i.e., IDH1/2 mutations) need further studies regarding the impact on GS treatment efficacy and prognosis,[11,22,33] Moreover, they seem to explain the cellular metabolism, DNA repair, and epigenetic regulation, which contribute to GS carcinogenesis.[33] These mutations are common in more than 80% of DLGG and are considered biomarkers in secondary GBM;[33] however, they are rare in primary GS and GBM.[11,29] It is interesting to observe that the presence of IDH mutation in some GS probably means that some of these rare tumors also may arise from a low-grade glioma and follow the course of secondary gliomagenesis like in GBM.

Both components (i.e., gliomatous and sarcomatous) of GS present tp53 mutations or overexpression and are found in patients with primary and secondary GS, suggesting that they may occur early in gliomagenesis.[20-22,45-48] These mutations increase the vulnerability to mesenchymal differentiation through cancer epithelial-to-mesenchymal transition-like processes that are also associated with cancer aggressiveness and could be a key in GS pathogenesis.[13,36] These mutations are rare in GS, however, some study findings slightly differed with these data, demonstrating tp53 positivity in the majority of lesions.[22,38,45] Our analysis showed an association between IDH1 and tp53 mutations in GS [Table 1]. The frequent DNA copy number losses in GS, mainly in regions containing CDKN2A genes (i.e., chromosomes nine and ten) that encode tumor suppressors and regulate the tp53 gene may explain why those mutations are so frequent in these tumors[30] and were related to treatment resistance and poor patient OS.[13]

Some studies suggest that ATRX is expressed in all GS.[35] ATRX maintains genome stability, gene expression, and cell cycle regulation. ATRX loss in elderly patients is associated with IDH-mutation in GBM. Despite that, it is not well established if this ATRX loss is more prevalent in primary or secondary GBM.[9,12,34]

TERT promoter mutations were majorly present in both glial and mesenchymal tumor areas in GS, and they play a crucial role by conferring these tumors unrestricted growth properties, contributing to the tumorigenesis.[4,27] Therefore, telomerase activation may be an underlying mechanism

Table 1: Molecular profile of patients presenting with gliosarcoma.

Authors (ref)	*n*	Median age (IQR)	Male sex (%)	Mean diameter (cm)	Tumor Location	IDH1 mutation (%)	TP53	TERT (% based on n of patients)	MGMT (% based on n of patients)	1p/19q codeletion	Ki67 index ≥23,0% (%)	Overall survival (months)
Adeberg *et al.*, 2016[1]	37	62.0 (42–82)	67.6	NR	NR	0	NR	70.3%	27.0%	NR	NR	13.4
Ahmed *et al.*, 2019[2]	11	63.0 (41.8–81.7)	64.0	3.85	NR	0	82%	NR	NR	NR	50%* (5/10)	12.6
Biernat *et al.*, 1995[6]	12	51.5 (32–52)	66.7	NR	NR	NR	16.6%	NR	NR	NR	NR	NR
Cachia *et al.*, 2015[8]	34	55 (35–74)	0.71	NR	18 temporal lobe; 14 frontal lobe; 7 parietal lobe; 3 occipital lobe	7.1% *(1/14)	57.1%* (8/14)	NR	NR	NR	NR	17.5
Cho *et al.*, 2017[13]	28	51.5 (42–64)	67.9	5.16	9 temporal lobe; 10 frontal lobe; 5 parietal lobe; 2 occipital lobe; 2 others	3,50	71.0%	NR	38.9%* (7/18)	35.3%* (6/17)	43.7% *(7/16)	12.0
Lee *et al.*, 2012[27]	26	51.0 (11–84)	61.5	NR	6 temporal lobe; 8 frontal lobe; 2 parietal lobe; 3 corpus callosum; 2 cerebellum; 2 multilobed; 1 frontotemporal; 1 cingulate gyrus; 1 parietal and corpus callosum	7.7	NR	NR	11.5%	NR	NR	11.3
Peckham *et al.*, 2019[38]	25	65 (52.5–74)	52.0	5.6	13 temporal lobe; 10 frontal lobe; 2 parietal/ occipital lobe	0	81.25%* (13/16)	NR	12.5%* (2/16)	NR	NR	8.25
Reis *et al.*, 2000[40]	19	56.0 (51–67)	57.9	NR	8 temporal lobe; 1 frontal lobe; 1 parietal lobe; 1 occipital lobe; 1 brainstem; 2 temporo-parietal; 1 temporo-occipital; 1 parietal-occipital; 2 cerebrum [1 case NR]	NR	26%	NR	NR	NR	NR	NR

*Values referring to the fractions of the patients in which the researches were carried out for a given biomarker. †Average value, data provided by the authors. *n*: Number of patients. NR: Not reported. IQR: Interquartile range

Table 2: Patients presenting with gliosarcoma in intraventricular location.

Authors (ref)	*n*	Median age (IQR)	Male sex (%)	Mean diameter (cm)	Tumor Location	Surgical Approach	Gross total resection	Cyst Component	IDH1 mutation (%)	ATRX	TP53	Ki67 index ≥23% (%)	Overall survival (months)
Baldawa *et al.*, 2013[5]	1	18.0	0	3	Temporal horn of the left ventricle and left atrium	Left temporal craniotomy (transtemporal transcortical - middle temporal gyrus)	No	Yes	NR	NR	NR	NR	4 (Alive)
Doddamani *et al.*, 2016[16]	1	23	100	6.23	Occipital horn of right lateral ventricle	Right parietal craniotomy (transcortical transventricular)	Yes	Yes	NR	NR	NR	NR	6 (Alive)
Govindan *et al.*, 2008[18]	1	55.0	0	NR	Septum and both frontal horns of lateral ventricles	NR	Yes	No	NR	NR	Positive in both components	NR	0.33 (Died)
Han *et al.*, 2008[19]	2	45 (36-54)	50	6.07	Left posterior horn of lateral ventricle	NR	NR	Yes	NR	NR	NR	NR	8 (Alive)
				4.33	Midline + bilateral intraventricular + corpus callosum	NR	NR	No	NR	NR	NR	NR	1 (Died)
Huo *et al.*, 2014[23]	1	47	100	4.33	Frontal lobe + anterior horn and body of left lateral ventricle	NR	NR	Yes	NR	NR	Positive in both components	0%	130.0 (Alive)
Moiyadi *et al.*, 2009[32]	1	65.0	100	NR	Right temporal horn	Right temporal craniotomy (transcortical)	No	No	NR	NR	Positive in both components	NR	2.0 (Alive)
Poyuran *et al.*, 2017[39]	1	68.0	100	NR	Frontal horn of right lateral ventricle	Right frontal craniotomy (transsulcal transventricular)	Yes	No	0%	Retained	Negative	NR	2.0 (Died)
Salunke *et al.*, 2017[41]	1	28.0	100	NR	Bilateral lateral ventricles	Parasagittal craniotomy (transcortical)	No	No	NR	NR	NR	NR	NR
Sarkar *et al.*, 2013[43]	1	60.0	0	NR	Septal region extending into body and frontal horn of both lateral ventricles	Right frontal craniotomy (transfrontocortical transventricular)	Yes	No	NR	NR	NR	NR	NR
Our case	1	44	100	5.02	Lateral ventricles trigone	Right parietal craniotomy (transparietal transsulcal)	No	Yes	100%	Intact/ Partial loss	100%	100%	2.76 (Died)

n: Number of patients, NR: Not reported, IQR: Interquartile range.

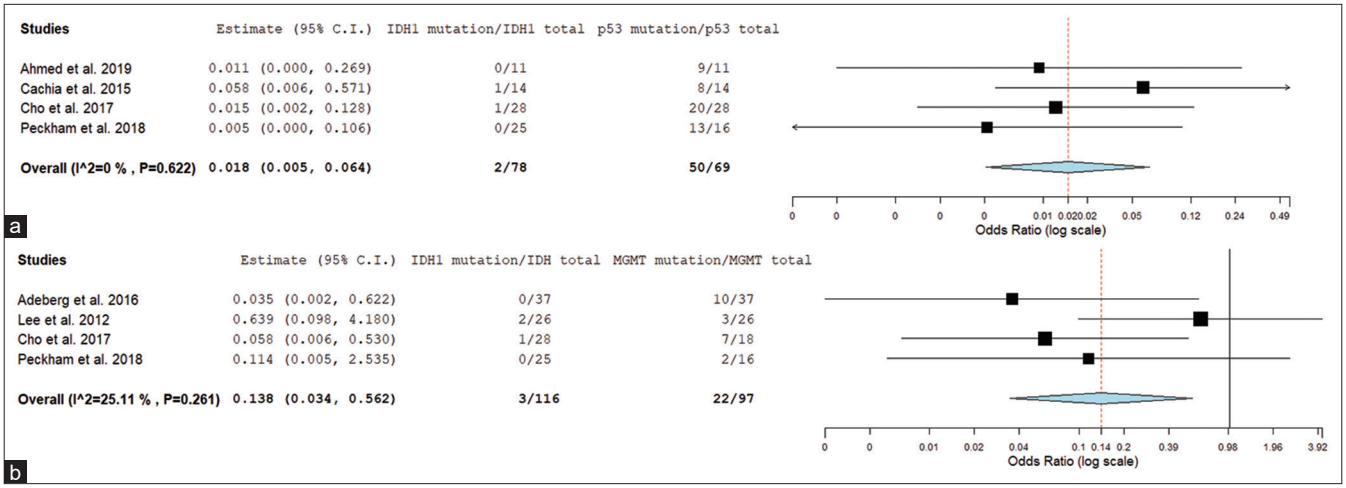

Figure 8: Forest plot of the molecular profile of gliosarcoma. (a) IDH1 versus p53. (b) IDH1 versus MGMT.

in GBM; moreover, TERT mutations are more frequent in IDH-mutant GBM and presented a better OS in these tumors.[27] 1p/19q codeletion is strongly associated with TERT mutations in malignant gliomas[7,27] and it is typically associated with mutations in IDH1/2.[31]

Ki-67 is a nonhistone nuclear protein and a cellular marker associated with ribosomal RNA transcription in cell proliferation[3,47] and the increasing Ki-67 expression may be the final event in the progression of these tumors.[10] Ki-67 index with values below 23% indicating better OS in GBM and IDH1 mutations were associated with low Ki-67 expression in primary GBM.[10]

MGMT is a DNA repair protein and its loss is correlated to increased survival in malignant gliomas.[25] However, the MGMT methylation may vary between GBM and GS which can impact overall and progression-free survival.[25,44] We observed that IDH1 mutations, a rare finding in GS (that is also correlated with better survival), are also associated with higher frequencies of methylated MGMT.

In our case, the tumor was in the atrium and the occipital horn of the lateral ventricles and we decided to achieve a maximal resection minimizing the risks to the relevant subcortical tracts through a transsulcal approach. A gross total resection of the tumor without significant complication requires a thorough understanding of available surgical approaches and their relative advantages and disadvantages.[14]

Limitations

We may point some relevant limitations in our paper.

Since there are many nonrecorded IDH1 statuses in prior studies in both overall and intraventricular group, the percentages as described may have errors.

Although we found a statistical correlation between IDH1 mutation and tp53 and between IDH1 mutation and MGMT, we must alert that with so few numbers of IDH1 positive cases data might be erroneous.

Due to the great limitation of data related to GS in the literature, many comparisons and analogies in the discussion were made in relation to GBM, including the cutoff point used for the Ki-67 of 23%, which is not entirely adequate because they are distinct pathologies, despite some similarities.

CONCLUSION

There is a lack of data in the literature related to molecular profiles specific to GS, with an inappropriate tendency to compare their behavior and molecular profile with GBM. More molecular studies are needed for GS.

We found a correlation between IDH1 mutation expression with p53 and MGMT expression in GS, and future studies exploring this molecular profile in GS are strongly encouraged.

Our study validates the need to perform IDH1 analysis in all GS cases and assess other molecular and clinical associations and outcomes, respectively.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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