Gliosarcoma: Report of Four Cases and Review of Literature

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Abstract

Gliosarcoma (GSM) is a rare central nervous system malignancy; it represents less than 0.5% of all intracranial tumors. GSM usually affects male in their fifth to sixth decade of life with supratentorial location especially in temporal lobes. The management of GS is extrapolated from glioblastoma with maximal gross total resection, and adjuvant radiotherapy with/without temozolomide. The prognosis is poor with median survival ranged from 06 to 14.8 months. The optimal treatment of GSM is unclear because of the lack of prospective studies. We report 04 cases (three cases of primary GSM and one case of secondary GSM) treated in our department of radiotherapy. Unfortunately, this publication confirmed the poor prognosis and the aggressive behavior of GSM tumors.

Keywords: Gliosarcoma, Glioblastoma, Radiotherapy.

INTRODUCTION

Gliosarcoma (GSM) is a central nervous system tumor composed of a mixture of malignant glial and sarcomatous elements [1, 2]. Stroebe described the first reported case in 1895 but it was not a widely accepted diagnosis until 60 years later when Feigin and Gross (1954) described three cases of gliosarcoma. They share genetic, clinical, and prognostic similarities with glioblastoma (GBM). Hence, it is not unusual that they are treated in a fashion similar to the GBM. Unfortunately, gliosarcoma is an aggressive disease with dismal outcomes [3]. It is more common in fifth and sixth decade of life with slight male preponderance [4]. In this paper, we analyzed the clinical, radiological, histopathological, and treatment-related aspects of GSM, treated in our department of radiotherapy, in the light of the existing literature.

OBSERVATIONS

Case 1

An 81-year-old male presented at emergency with headache, speech disorder, mouth deviation and left hemibody weakness. Neurologic examination revealed left hemiparesis with facial paralysis. Magnetic resonance imaging (MRI) was performed and showed a heterogeneous right temporoparietal mass measuring 46 x 48 x 51 mm with double components (cystic and solid) (Figure 1) and an important perilesional edema with moderate mass effect.

A stereotaxic biopsy of the mass was performed. Histopathological with immunohistochemistry (IHC) examination detected tumor disposed in sheets showing pleomorphic cells displaying anisomorphic nuclei, frequent mitosis with areas of spindle tumor cells displaying anisoneucleosis. Foci of reticulin-rich tumor cells suggested sarcomatous component. Glial fibrillary acidic protein (GFAP) positive tumor cells seen in glial component and interspersed glial GFAP negative tumor cells suggest sarcomatous component revealed a gliosarcoma (Figure 2). The patient has been excused from surgery due to his age and altered general condition. Then, he was referred to radiotherapy.

A hypofractionated radiation therapy was adopted with volumetric modulated arc therapy technique (VMAT). A total dose of 40, 05 gray in 15 fractions (2, 67 Gy per fraction) was delivered to the Clinical Target Volume (CTV) defined as the enhancing regions on T1 weighted sequence with a 15 mm expansion (accounting for anatomic boundaries). The planning target volume (PTV) was created by adding geometric margins of 5 mm to the CTV (Figure

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3). Unfortunately, the patient passed away two months after the completion of radiotherapy course.

**Case 2**

A 36-year-old female presented to neurosurgery department with complaints of headache, vomiting and recent history of generalized seizures. Magnetic resonance imaging (MRI) of brain showed heterogeneously enhancing right temporo-parietal mass of 41 x 41 x 46 mm with perilesional edema and moderate mass effect shifting the left lateral ventricle (Figure 2). A left-side temporo-parietal craniotomy and maximal macroscopic resection were performed without inducing neurological deficit. Histopathological and IHC examination revealed gliosarcoma. Post-operative MRI showed a nodular residual disease. The patient was referred for adjuvantradiotherapy. He was irradiated using VMAT technique to a total dose of 60 Gy in 30 fractions. The target volumes were as follows: the CTV defined as the enhancing areas on T1 weighted sequence and postoperative cavity with a 20 mm expansion (accounting for anatomic boundaries) including perilesional edema (high signal intensity in T2 weighted sequence on T2 sequence). The PTV was generated by adding geometric margin of 5 mm to the CTV. In association of radiotherapy, temozolomide at doses of 75 mg/m2 per day was administered in concomitant setting. The patient was lost to follow-up and she did not receive adjuvant temozolomide. She died five months after completion of adjuvant radiotherapy.

**Case 3**

A 48-year-old male consulted for vertigo, headache and more recently seizures. Neurological examination was normal. Brain Magnetic resonance imaging (MRI) showed a Right temporal process measuring 32 mm with associated Edema (Figure 5 A, B, C). A complete macroscopic resection was performed. Histopathological examination revealed glioblastoma. The patient was referred to our department and underwent a post-operative radiotherapy treatment receiving a total dose of 60Gy in 30 fractions and concurrent temozolomide 75mg/m2 per day. Adjuvant temozolomide therapy was delivered for six months (150mg/m2 per day 5 days per month).

Sixteen months after the completion of radiotherapy, the patient developed a severe headache, a decreased visual acuity, memory problems, sixth nerve palsy and left hemiparesis. Brain MRI showed a right temporo-parietal process, high signal intensity in Flair sequence, measuring 72 x 56 mm with mass effect on right lateral ventricle and shift of the midline structures (Figure 5 D, E). Total surgical excision was undertaken, but Post-operative CT scan showed residual disease in the inner surface of the cavity (Figure 5F). Histopathological examination showed a cerebral parenchyma infiltrated by a biphasic tumoral tissue pattern with alternating areas displaying glial and mesenchymal differentiation. The gliomatous component strongly GFAP positive was intermingled with the sarcomatous tumor cells that demonstrated a vimentine expression. A diagnosis of GSM was established. The patient received chemotherapy with a basis of bevacizumab 10mg/kg every 2 weeks and irinotecan 125 mg/m2 every 2 weeks. The patient died from tumor progression after two cycles, approximately 27 months after the diagnosis of GB was made.

**Case 4**

A 46 year-old female, receiving treatment for arterial hypertension, presented to neurosurgery department with a weakness of the right side of the body and generalized seizures evolving for one month. Neurologic examination revealed Glasgow score of 15, right hemiparesis without facial paralysis. MRI detected a left temporo-parietal mass of 31 x 29 x 40 mm with surrounding edema (Figure 6). A left-side temporo-parietal craniotomy with maximal macroscopic resection was performed. Histopathological exam of the tumor revealed a gliosarcoma. The neurological status remained stable and No residual mass was detected in Post-operative MRI. Adjuvant Radiotherapy using VMAT technique was performed. The patient received a total dose of 60Gy in 30 fractions with concurrent temozolomide (75 mg/m2 per day). The target volumes were as follows: the CTV defined as the residual post-operative cavity with any enhancing areas. Then, a 20 mm expansion (with inclusion of perilesional edema was applied (accounting for anatomic boundaries). The PTV was generated by adding geometric margin of 5 mm to the CTV. Two cycles of adjuvant temozolomide were administrated with a slight improvement in his neurological condition.
Fig-1: Axial T1-weighted contrast-enhanced MRI showing a enhancing mass in the right temporo-parietal region

Fig-2: (a) Tumor disposed in sheets showing pleomorphic cells displaying anisomorphic nuclei, frequent mitosis (H and E, ×100). Areas of spindle tumor cells displaying anisonucleosis are also noted (b) (H and E, ×200). Foci of reticulin-rich tumor cells (c: Reticulin, ×40) suggest sarcomatous component. Glial fibrillary acidic protein (GFAP) positive tumor cells seen in glial component and interspersed glial GFAP negative tumor cells suggest sarcomatous component (d and e: GFAP, ×200)

Fig-3: axial (a) and coronal (b) computed tomography scan dosimetry showing a conformal dose distribution (isodose 95%) by RapidArc
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Fig-4: Axial T1-weighted contrast-enhanced MRI (a) and Flair MRI (b) showing a heterogeneously enhancing mass in the right temporoparietal region

Fig-5: A: axial, B: Coronary and D: sagittal MRI images showed a Right temporal process corresponded to a glioblastoma. D: Axial and E: Coronary MRI image of a secondary gliosarcoma, at the same location of the previously treated GBM. F: axial CT, performed after the total resection of the gliosarcoma

Fig-6: Axial T1-weighted contrast-enhanced (a) and Flair (b) MRI showing a temporo-parietal mass with surrounding edema
DISCUSSION

Gliosarcoma was first reported by Strobe in 1895 but did not gain wide acceptance until 1955 when Feigen and Gross defined as a subtype of glioblastoma. GS has been reported to constitute less than 0.5% of all intracranial tumors [5, 6]. It can be primary or secondary. Secondary GSM is rare, developed usually within 1-year of GBM treatment (surgery, radiation, chemotherapy). While radiation-induced GSM developed many years (5.2 years) after irradiation for other brain tumors like meningioma, low-grade glioma, medulloblastoma, etc. In this publication, one of the three patients presented a secondary gliosarcoma after treatment of glioblastoma.

GSM usually affects people in their fifth to sixth decade of life with a consistent male predominance and the most common symptom was headache due to raised intracranial pressure [7]. The median age of patients was 55 years with equal gender distribution. Headache was the most consistent symptom.

Numerous reports have mentioned about the tendency of GSM to affect supratentorial cerebral lobes and particularly temporal lobes [4, 8, 9]. In our experience, all patients had supratentorial tumors and temporal lobe was the most frequently involved site. In addition to temporal lobe affinity, GSM has also been reported to affect peripheral parts of the brain [8]. It can be characterized by specific radiological features when compared to glioblastoma. Yi et al. examined MRI images of 48 GSM patients. Several variables were more commonly found in GSM MRIs, when compared to GBM, including hemorrhage, salt-and-pepper sign, and unevenly thickened walls, intratumoral large feeding artery and eccentric cystic portion [10].

For histopathological diagnosis of GS, Meis [2] laid down certain characteristics. These include: (a) The tumor must be bimorphic that is composed of two morphologically distinct malignant cells population; (b) one component must be astrocytic with areas of necrosis, fulfilling the criteria for GBM; (c) the sarcomatous component must resemble a spindle cell sarcoma; and (d) a minimum of one confluent sarcomatous area must fill one medium power field (10 objective with 10 eyepiece). Immunohistochemistry helps differentially visualize the bimorphic areas as GFAP stains gliomatous areas while reticulin positively stains sarcomatous areas.

The management data of gliosarcoma are sparse, and it is extrapolated from GBM. Several studies have been conducted to study the effect of multi-modality treatment on the outcome of GSM. In Castelli’s study, 75 patients between the ages of 23–79 years were treated with a combination of surgery (n=66), TMZ (n=58) and radiotherapy (n=72). OS of two years was achieved in 12% of the patients (95% CI 4–20%) and the median OS was 13 months [13]. Similarly, Kozak et al.’s epidemiological study demonstrated the positive outcome of multimodality treatment: tumor resection (not biopsy only) along with adjuvant RT correlated with an increase in OS [14]. Conversely, in a study conducted by Alfredo et al., combined multimodal therapy did not show improvement in OS [15]. Current guidelines set by the national comprehensive cancer network (NCCN) state that maximal safe surgical resection followed by RT with concurrent and adjuvant TMZ is recommended for GSM treatment [12]. Because of frequent peripheral location, GSM offers a better chance of gross total excision when compared with GBM.

Most studies point toward a dismal survival in these patients which is worse compared to GBM. The median survival has been reported to range from 06 to 14.8 months [16-18]. The overall survival of patients in this study was 05 months.

Fadi Saadeha et al. [19] identified some prognostic factors including age, preoperative KPS, (radiologic/ intraoperative) impression of meningioma versus GBM, extent of excision, and adjuvant chemoradiation. Younger age, good preoperative KPS (which ensures that the patient undergoes the entire treatment modalities) and gross total excision as opposed to lesser degree of excision are associated with better survival, facts that are similar to the GBMs. It fits perfectly with our experience since the best outcome was noted at the younger patient.

GS with meningioma like features tends to have a better survival. The reason for this difference was the better extent of excision in meningioma like GS compared to GBM like GS. Salvati et al. [20] was the first to report a significant difference in the survival between these two groups. This fact was reported in the current series.

Gliosarcoma is a rare central nervous system malignancy that affects younger patients compared to GBM with a stronger male predilection. Clinically, they are nearly indistinguishable from GBM. Maximal safe resection followed by radiotherapy and chemotherapy (TMZ) appears to be the best current treatment for these tumors. Unfortunately, this publication confirmed the poor prognosis and the aggressive behavior of GSM tumors. A consensus on the optimal treatment for GSM patients is unclear because of the lack of prospective studies.

LIST OF ABBREVIATIONS
GBM: glioblastoma
GSM: gliosarcoma
TMZ: temozolomide
GY: gray
CTV: clinical target volume
IHC: immunohistochemistry
VMAT: volumetric modulated arc therapy
GFAP: glial fibrillary acidic protein
MRI: magnetic resonance imagery
OS: overall survival

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