

GLIOSARCOMAS: The Rising Trend

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Abstract: Introduction: Gliosarcomas are rare tumors of the central nervous system which are highly malignant. They have a very poor prognosis. The epidemiology and natural history of Gliosarcomas are similar to Glioblastoma multiforme. Males are more frequently affected than females (M:F ratio 1.8:1). It is recognized that gliomas can induce sarcomatous transformation in the supporting mesenchymal elements. It affects the temporal lobe more often. The diagnosis of gliosarcoma is based on a biphasic tissue pattern composed of two distinct malignant cells, one component being gliomatous and the other one being malignant mesenchymal differentiation. Materials and Methods: We analysed 6 cases of Gliosarcoma. 3 cases were Primary Gliosarcoma and 3 cases were seen in Glioblastoma multiforme patients who developed recurrence. Patients age ranged from 34 – 60 yrs. Male: Female ratio was 5:1. All patients underwent tumor excision and received adjuvant radiotherapy and chemotherapy. Treatment: Patients underwent maximal safe resection and received adjuvant radiotherapy with Tab. Temozolomide 75 mg/ m² daily, followed by adjuvant chemotherapy (Temozolomide 150 mg/m² OD x 5days -6 cycles). The 3 Primary Gliosarcoma patients received IMRT of dose 60 Gy/ 30 fr. The 3 GBM patients who developed recurrence and the histology were gliosarcoma received a dose of 50 Gy/25 fr. Results: The median survival of Gliosarcoma was 14.6 m in this case series which is slightly better than the median survival of 9m in most of the other reports. The median survival of PGS was better than the patients who developed recurrence (19.6 m v/s 9.6 m). In patients who developed recurrence; there were 2 deaths and 1 in PGS due to disease progression. Conclusion: Clinically Gliosarcoma presents the same way as Glioblastoma multiforme. Prognosis is almost the same as GBM. Patients who undergo tumor excision followed by adjuvant radiotherapy and chemotherapy have better survival outcomes. The Incidence of developing Gliosarcoma in recurrence cases is showing a rising trend.

Keywords: PGS: Primary Gliosarcoma, SGS: Secondary Gliosarcoma, GBM: Glioblastoma Multiforme, WHO: World Health Organization, GFAP: Glial Fibrillary Acid Protein, IMRT: Intensity Modulated Radiotherapy

1. Introduction

Gliosarcomas are rare tumors of the central nervous system which are highly malignant. They have a very poor prognosis. Gliosarcoma was initially described by Stroebe in 1895. It is a brain neoplasm consisting of both glial and mesenchymal components⁽¹⁾.

The 2007 World Health Organization (WHO) classification scheme places Primary Gliosarcoma (PGS) as a Grade IV neoplasm and a variant of Glioblastoma multiforme (GBM). It is a well-circumscribed lesion with clearly identifiable biphasic glial and metaplastic mesenchymal components⁽²⁾. It accounts for 2-8% of all Glioblastoma multiforme (GBM) and 0.48% of all intracranial tumors^(3,4). According to the 2010 statistical analysis by the Central Brain Tumor Registry of the United States, from 2004 to 2006, GBM accounted for 53.8% of all Gliomas, Gliosarcomas accounted for 2% of all GBM.

The epidemiology and natural history of Gliosarcomas are similar to Glioblastoma multiforme^(5,6,7). Males are more frequently affected than females (M:F ratio 1.8:1). It is recognized that gliomas can induce sarcomatous transformation in the supporting mesenchymal elements. It affects the temporal lobe more often. It is difficult to differentiate High grade glioma, CNS Lymphoma and metastatic carcinoma radiologically and clinically.

2. Pathogenesis

The Pathogenesis of Gliosarcoma is controversial and has many theories. It suggests that the sarcomatous components

originated from neoplastic transformation of hyperplastic blood vessels commonly found in High grade gliomas. Studies showing histological reactivity of the sarcomatous component to vascular endothelial markers such as factor VIII, Von Willebrand factor and CD34 provided support for this hypothesis⁽⁸⁾.

Monoclonal origin theory suggests originating of both components of gliosarcoma, with the sarcomatous component via aberrant mesenchymal differentiation of the malignant glioma. Other studies have demonstrated mutations in p53 and PTEN, CDK amplification, p16 deletion. In primary Gliosarcomas-EGFR, MDM2, P53 (binding and inactivation protein) amplification and over expression are some of the features⁽⁹⁾.

Few Studies have also found a much lower frequency of EGFR amplification in Gliosarcoma than in primary GBM. While EGFR is amplified in up to half of primary GBMs, the rate of amplification is much lower in Gliosarcoma (8% in small series).

Secondary Gliosarcomas were reported during recurrences after the patients received radiation. The genetic alterations associated were PTEN mutation, P16 deletion and TP53 mutation and lack EGFR amplification (0% - 8%). The genetic changes in Gliosarcomas are intermediate-between primary and secondary GBM⁽¹⁰⁾.

3. Histopathology



Gliosarcoma: Shows pleomorphic tumor cells with areas of necrosis and spindle cells with pleomorphic nucleus (sarcomatous).

IHC: Presence of glial fibrillary acid protein, Vimentin, Desmin, Ki 67 index-60%.

The diagnosis of gliosarcoma is based on a biphasic tissue pattern composed of two distinct malignant cells, one component being gliomatous and the other one being malignant mesenchymal differentiation. There can be variants of herring bone pattern of fibrosarcoma, malignant osteoid cells, cartilaginous differentiation of an osteosarcoma or chondrosarcomal differentiation ⁽¹¹⁾. Gliosarcoma must also be differentiated from Gliofibroma in which the mesenchymal component is benign,

4. Materials and Methods

We analysed 6 cases of Gliosarcoma. 3 cases were Primary Gliosarcoma and 3 cases were seen in Glioblastoma multiforme patients who developed recurrence.

Age: Patients age ranged from 34 – 60 yrs. Male: Female ratio was 5:1. All patients underwent tumor excision and received adjuvant radiotherapy, chemotherapy.

Treatment

Patients underwent maximal safe resection and received adjuvant radiotherapy with Tab. Temozolomide 75 mg/ m² daily, followed by adjuvant chemotherapy (Temozolomide 150 mg/ m² OD x 5days -6 cycles) ⁽¹²⁾.

The 3 PGS patients received Intensity modulated radiotherapy of dose 60 Gy/ 30 fr ⁽¹⁴⁾.

The 3 GBM patients who developed recurrence and the histology was gliosarcoma received a dose of 50 Gy/25 fr by Intensity modulated radiotherapy.

Target volumes were prescribed according to the RTOG trials 98-03 and 08-25 which recommended volumes: CTV1 = surgical bed and/or residual tumor +20–25mm, CTV2 = surgical bed and/or residual tumor +5mm. The planning target volume (PTV) is an additional margin of 3–5mm. For patients who developed recurrences, reirradiation was done. Dose given was 50 Gr/25 fr. Planning target volume consisted of CTV + 5mm margin.

Patients underwent weekly hemogram and biochemistry during radiation and monthly hemogram and biochemistry during adjuvant chemotherapy. Patients were followed up every 3 monthly and evaluated by CT/MRI scans, Brain SPECT scans was also done to know the viability of tumor.

Table 1: Patient's characteristics

Number	Age (Yrs)	Sex (M/F)	Histology	Response Assessment	Survival
case 1	52	M	Primary Gliosarcoma	Progressive disease	18
case 2	45	M	Primary Gliosarcoma	Progressive disease (death)	19
case 3	40	M	Primary Gliosarcoma	NED	22
case 4	48	F	Secondary Gliosarcoma	Progressive disease (death)	9
case 5	60	M	Secondary Gliosarcoma	Small residual disease present	16
case 6	34	M	Secondary Gliosarcoma	Progressive disease (death)	4

5. Results

The median survival of Gliosarcoma was 14.6 months in this case series, which is slightly better than the median survival of 9 months in most of the reports. The median survival of Primary Gliosarcoma was better than the patients who developed recurrences (19.6 months v/s 9.6 months). There were 2 deaths in patients who developed recurrence and 1 Primary Gliosarcoma patient died due to disease progression.

6. Conclusion

Clinically Gliosarcoma presents the same way as Glioblastoma multiforme. Prognosis is almost the same as GBM. Patients who undergo tumor excision followed by adjuvant radiotherapy and chemotherapy have better survival outcomes. The Incidence of developing Gliosarcomas in recurrence cases is showing a rising trend. Diagnosing this rare variant of high grade gliomas at the

earliest and treating optimally will improve the overall survival in this devastating disease.

7. Discussion

Gliosarcomas are rare variant in Glioblastoma multiforme. The treatment is on the same lines as Glioblastoma⁽¹⁵⁾. Diagnosing the gliosarcoma must be done meticulously as it can be mistaken for metastatic carcinoma or CNS lymphoma. Gliosarcoma and Glioblastoma multiforme cannot be distinguished clinically. Micro dissection genotyping is segmented as a molecular technique to better characterize these tumors⁽¹⁶⁾.

Patients must undergo tumor excision and should receive adjuvant radiation with Tab. Temozolomide 75 mg/ m² OD followed by adjuvant chemotherapy (Temozolomide 150 mg/m² OD x 5 days for 6 months). Contrary to the belief that Gliosarcoma fares worse than Glioblastoma, if patients are treated optimally with Radiotherapy and Chemotherapy (Temozolomide 75 mg/m² OD) and Adjuvant Chemotherapy (Temozolomide 150 mg/m² OD x 5 days for 6 months), the prognosis remains almost the same as Glioblastoma patients. Age, Extent of resection, Use of adjuvant radiotherapy and chemotherapy are the important variables in improving survival in this devastating disease⁽¹⁷⁾. Further the EGFR expression, MGMT methylation, IDH1 mutation must also be analysed to explore the scope of various other chemotherapeutic agents.

8. Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

- [1] Stroebe H. Ueber Entstehung und Bau der Gehirnglioma. Beitr Pathol Anat Allg Pathol. 1895;19:405–486.
- [2] Louis D, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P. The 2007 WHO classification of tumours of the Central nervous system. *Acta Neuropathol*. 2007;114:97–109.
- [3] Meis JM, Martz KL, Nelson JS. Mixed glioblastoma multiforme and sarcoma. A clinicopathologic study of 26 radiation therapy oncology group cases. *Cancer* 1991;67:2342–2349.
- [4] Morantz RA, Feigin I, Ransohoff J. Clinical and pathological study of 24 cases of gliosarcoma. *J Neurosurg* 1976;45:398–408.
- [5] Galanis E, Buckner JC, Dinapoli RP, et al. Clinical outcome of gliosarcoma compared with glioblastoma multiforme: North Central Cancer Treatment Group results. *J Neurosurg*. 1998;89:425–430.
- [6] Sarkar M, Sharma MC, Sudha K, Gaikwad S, Varma A. A clinico-pathological study of 29 cases of gliosarcoma with special reference to two unique variants. *Indian J Med Res*. 1997;106:229–235.
- [7] Parekh HC, O'Donovan DG, Sharma RR, Keogh AJ. Primary cerebral gliosarcoma: report of 17 cases. *Br J Neurosurg*. 1995;9:171–178.
- [8] Sreenan J, Prayson RA. Gliosarcoma: a study of 13 tumors, including p53 and CD34 immunohistochemistry. *Arch Pathol Lab Med*. 1997;121:129–133.
- [9] Biernat W, Aguzzi A, Sure U, Grant JW, Kleihues P, Hegi ME. Identical mutations of the p53 tumor suppressor gene in the gliomatous and the sarcomatous components of gliosarcomas suggest a common origin from glial cells. *J Neuropathol Exp Neurol*. 1995;54:651–656.
- [10] Reis RM, Köni-Leblebicioglu D, Lopes JM, Kleihues P, Ohgaki H. Genetic profile of gliosarcomas. *Am J Pathol* 2000; 156: 425–432.
- [11] Ohgaki H, Biernat W, Reis R, Hegi M, Kleihues P. Gliosarcoma. In: Kleihues P, Cavenee WK (eds). *Pathology and Genetic of Tumors of the Nervous System*, 2nd edn. Lyon: IARC Press, 2000; 42- 44.
- [12] Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987–96.
- [13] Mason WP, et al. Canadian recommendations for the treatment of glioblastoma multiforme. *Curr Oncol* 2007;14(3):110–7.
- [14] Fuller CD, Choi M, Forthuber B, Wang SJ, Rajagiriyl N, Salter BJ, et al. Standard fractionation intensity modulated radiation therapy (IMRT) of primary and recurrent glioblastoma multiforme. *Radiat Oncol* 2007;2:26.
- [15] Galanis E, Buckner JC, Dinapoli RP, et al. Clinical outcome of gliosarcoma compared with glioblastoma: North Central Cancer Treatment Group results. *J Neurosurg* 1998;89:425–30.
- [16] John A Ozolek, Sydney D Finkelstein and Marta E Couce. Gliosarcoma with epithelial differentiation: immunohistochemical and molecular characterization. A case report and review of the literature. *Modern Pathology* 2004; 17, 739-745.
- [17] Kevin R. Kozak, Anand Mahadevan, and John S. Moody Adult gliosarcoma: epidemiology, natural history, and factors associated with outcome. *Neuro Oncology* 2009;11, 183-191.