PEDIATRIC GLIOSARCOMA- CASE REPORT AND REVIEW OF LITERATURE

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Abstract:
Aim- To report a case of Pediatric Gliosarcoma. Case history- A 11 year old boy was referred to the Neurology department for complaints of progressive weakness of left upper and lower limb and deviation of face to right side since 2 months and headache and vomiting for 2 days. Patient had a past history one and a half years ago of convulsions of left lower limb and MRI Brain had suggested a granulomatous lesion in right Frontoparietal region 1x1.4 cms with edema. Patient was diagnosed as Neurocysticercosis and treated with Albendazole and Phenytoin and was asymptomatic for a year. Examination of the patient revealed a KPS 70 as patient needed support while walking, left hemiparesis (power 3 by 5) and left UMN facial palsy and increased ICT. CT Brain showed an irregular heterodense mass in right Frontoparietal region 6x5 cms with midline shift and significant edema. A subtotal excision was undertaken. Pathological review revealed a biphasic tumour with increased cellularity, mitotic index and necrosis with malignant spindle cells in Herring bone pattern. IHC showed diffuse positivity for Vimentin and focal for GFAP while SMA was negative. A diagnosis of Gliosarcoma - a rare variant of glioblastoma with sarcomatous elements- was made and the patient was treated with Radiotherapy 54 Gy (50.4 Gy with 3.6 Gy boost) with concomitant temozolamide 100 mg on all 42 days and is currently on adjuvant temozolamide 250 mg for 4 days a month. Patient is able to walk without support but facial asymmetry persists and left limb power is 4 by 5.

Conclusion:
-Gliosarcoma in the pediatric age group is a rare, aggressive malignancy and must be differentiated from the less aggressive gliofibroma. It must be treated on the lines of glioblastoma multiforme with concurrent and adjuvant temozolamide.

Keyword: Gliosarcoma, Pediatric, Vimentin, GFAP, Glioblastoma, Temozolomide, Radiotherapy
PEDIATRIC GLIOSARCOMA- CASE REPORT AND REVIEW OF LITERATURE

**AIM** - To report a case of Pediatric Gliosarcoma and review literature

**CASE HISTORY** - A 11 year old boy was referred to the Neurology department for complaints of progressive weakness of left upper and lower limb and deviation of face to right side since 2 month and headache and vomiting for 2 days. Patient had a past history one and a half years ago of convulsions of left lower limb and MRI Brain had suggested a granulamatosus lesion in right Fronto-parietal region 1x1.4 cms with edema(Fig. 1).

**Fig 1 - PREVIOUS MRI**

Patient was diagnosed as Neurocysticercosis and treated with Albendazole and Phenytoin and was asymptomatic for a year. There was no other significant history. Examination of the patient revealed a KPS of 70 as patient needed support while walking, left hemiparesis (power 3/5)and left UMN facial palsy and increased ICT. CT Brain showed an irregular heterodense mass in right Fronto-parietal region 6x5 cms with midline shift and significant edema (Fig. 2). A subtotal excision was undertaken (Fig. 3).

**Fig 2- PRE-OP CT**

**Fig 3-SUBTOTAL EXCISION DONE**

Pathological review revealed a biphasic tumour with increased cellularity, mitotic index and necrosis (Fig. 4) with malignant looking spindle cells in Herring bone pattern (Fig. 5).

**Fig 4**
IHC showed focal for GFAP (Fig. 6) and diffuse positivity for Vimentin (Fig. 7) while SMA was negative.

A diagnosis of Gliosarcoma - a rare variant of glioblastoma with sarcomatous elements - was made and the patient was treated with Radiotherapy 54 Gy (50.4 Gy to tumour + edema + 2 cm margin with 3.6 Gy boost to tumour + 2 cm margin in 180cGy/#, 30#, 6 weeks) with concomitant temozolamide 100 mg on all 42 days and is currently on adjuvant temozolamide 250 mg for 4 days a month. Patient is able to walk without support but facial asymmetry persists and left limb power is 4/5. Patient is on regular physiotherapy and is yet to resume schooling.

**DISCUSSION:**
Gliosarcoma is a rare variant of Glioblastoma multiforme with sarcomatous component. Most studies report that GS constitutes 2% of all GBMs while Morantz et al. and Kumar et al. claimed 8% incidence. It was originally described by Heinrich Stroebe et al in 1895. It is diagnosed histopathologically by glial components - nuclear pleomorphism, endothelial proliferation, increased mitotic activity and necrosis along with mesenchymal malignant spindle or round cells. The confirmation is by Immuno-histochemistry showing dual positivity for Glial fibrillary acid protein and a mesenchymal marker - Desmin, Vimentin, SMA etc. Regarding the cell of origin, in 1955, Feigin et al, reviewed several gliosarcoma cases and proposed that the endothelial hyperplasia of cerebral blood vessels within the high grade glial tumors may represent the malignant sarcomatous component. However, immunohistochemical studies have failed to detect endothelial markers in the sarcomatous...
component\textsuperscript{5,7}. The presence of identical p53 mutations and similar chromosomal imbalances and cytogenetic alterations in both gliomatous and sarcomatous components strongly supports the concept of a monoclonal origin of gliosarcomas. Some studies have shown expression of monohistiocytic markers, suggesting that gliosarcomas develop from histiocytes, whereas others suggest an origin from fibroblasts, pluripotent mesenchymal cells of the perivascular adventitia, or perivascular spaces\textsuperscript{7,1}. The most common predominant histologic picture of the sarcoma component is fibrous histiocyteoma, however, descriptions of osteoid, chondroid, myxoid, lipoid, as well as smooth and skeletal muscle have been reported\textsuperscript{7,1}. In 2000, WHO included gliosarcoma in their classification for malignant gliomas and was given an ICD code (ICD-O 9442) while 9440 is for GBM. Kozak et al. reported in 2009 retrospective data from SEER database comparing GBM and GS over a 16 yr period from 1988 to 2004. Their analysis included 16035 GBM and 353 GS patients\textsuperscript{8}. GS is similar to GBM in many ways namely age at presentation, gender predilection, racial distribution, tumour size at diagnosis\textsuperscript{10}, duration of symptoms\textsuperscript{10}, clinical features, radiological features\textsuperscript{14}, prognostic factors and overall survival. The usual age of presentation is in fifth to seventh decade. They are slightly more common in males (1.8:1). The 3 main prognostic factors are age at diagnosis, extent of surgical resection and use of Radiotherapy\textsuperscript{8}. The median survival of GS patients younger and older than 50 yrs is 15 months and 7-11 months respectively. The more the excision, better was the survival but there was no difference between subtotal excision and total excision. Median survival of GS patients receiving and not receiving RT was 4 and 10 months respectively.

Lutterbach et al.\textsuperscript{10} and Perry et al.\textsuperscript{13} concluded that pre-treatment KPS \textgreater 70 as a good prognostic factor. Salvati et al.\textsuperscript{14} concluded that those tumour with radiological findings of similar to meningioma and a higher sarcomatous element have a better prognosis. The only difference between GBM and GS is the location of primary. While most tumours are supra-tentorial, temporal lobe is the most common location (35-50\%) followed by parietal, frontal and occipital lobes\textsuperscript{11,15}. The management of GS is similar to GBM and safe maximal resection and radiotherapy are crucial to prolong disease free and overall survival. Regarding the role of chemo-radiotherapy and adjuvant chemotherapy, Morantz et al.\textsuperscript{12} reported a 3 week increase in survival (33 vs 36 weeks) which was not significant while Meis et al.\textsuperscript{11} also reported a 4 week non-significant increase in survival with various agents – BCNU, dacarbazine, misonidazole, semustine). Temozolomide was tried in 4 of the patients of the Salvatti et al. study but the study was not powered enough to analyse the benefit of temozolamide with radiotherapy though they concluded that chemotherapy along with radiotherapy improved survival marginally\textsuperscript{14}. The benefit of temozolomide in GBM was shown in the landmark trial by Stupp et al. who showed a significant 5-year survival benefit with concurrent and adjuvant temozolomide in newly diagnosed GM patients\textsuperscript{18}. Pediatric gliosarcomas (age 0 – 21 years) are ever rarer and a total of 23 cases have been reported in English medical scientific literature\textsuperscript{6}. A review of clinical and epidemiological characteristics of pediatric gliosarcomas has been reported by Karremann.
and is the only review available. The male:female ratio was reported as 1.2:1 and the mean age at diagnosis was 11 years. 6 out of 23 (26%) patients were < 3 years while 6 (26%) other patients had a history of prior therapeutic radiation to the brain. The most common presenting was of increased intracranial tension of mean 0.7 month duration. 60% of the patient series had a gross total resection and the median disease free and overall survival was 9.8 and 12.1 months respectively.

Another entity which could be misdiagnosed as gliosarcoma especially in the 0-20 year age group is gliofibroma, which has benign mesenchymal elements with dense desmoplastic reaction around the malignant glial cells. This tumour however has an insidious onset, longer duration of symptoms and a prolonged survival. This exceptionally rare neoplasm was first described in 1978 by Friede et al. and so far only 30 cases have been reported, and of those, only four have involved intracranial lesions in patients older than 20.

In the case presented by us, the insidious onset and prolonged duration and survival may suggest a Gliofibroma, however the histopathological review suggests a malignant mesenchymal tumour and the immunohistochemistry study was strongly positive for Vimentin suggesting gliosarcoma. So this patient with GS who received sub-total excision, high dose EBRT (54Gy) with temozolomide for 42 days and presently on adjuvant temozolomide appears to have responded well to treatment. This policy was decided upon by the tumour board in view of limited literature on chemotherapy for pediatric GS, the significant survival benefit for temozolomide with radiotherapy in GBM and the non-feasibility of obtaining MGMT promoter methylation for the patient.

CONCLUSION - Gliosarcoma in the pediatric age group is a rare, aggressive malignancy and must be differentiated from the less aggressive gliofibroma. It must be treated on the lines of glioblastoma multiforme as in adults.

REFERENCES


