

Glioblastoma multiforme: A pediatric case series

Marina S. Yacob, Donna L. Johnston

ABSTRACT

Introduction: Glioblastoma multiforme (GBM), the most aggressive malignant primary brain tumor, is uncommon in children accounting for only 3% of primary pediatric brain tumors. We reviewed a case series of five pediatric patients diagnosed at our institution over an 8-month period. **Case Series:** Of the five pediatric GBMs, three were supratentorial, one was infratentorial and one was in the spinal cord. The diagnosis of GBM occurred at a mean age of 9.25 years and the male to female ratio was 3:2. The main presenting symptoms included headaches (60%), nausea and vomiting (40%) and limb weakness (40%). Four of five patients were treated with maximal surgical resection and radiation therapy. The majority also received chemotherapy with temozolomide and lomustine. All patients died of tumor progression with a median survival of 9.0 months following diagnosis. **Conclusion:** Glioblastoma multiforme remains a very challenging tumor to treat in the pediatric population. Locally, the incidence of glioblastoma multiforme is increasing and further study needs to investigate if this is a national occurrence.

Keywords: Brain tumor, Glioblastoma multiforme, Oncology, Pediatric

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INTRODUCTION

Glioblastoma multiforme (GBM) is the most aggressive malignant primary brain tumor with an incidence of 2–3 per 100,000 people in the United States and Europe [1]. The glioblastoma multiforme (GBM), increase in frequency with age, mostly affecting adults between the 6th and 8th decade, and more commonly affecting men (male:female ratio of 3:2) [2]. The GBMs are uncommon in children, accounting for only 3% of childhood brain tumors [1–6].

This case series review was conducted at the Children's Hospital of Eastern Ontario (CHEO) located in Ottawa, Ontario, Canada. The CHEO is a medium sized program with 70–75 new diagnoses of malignancy each year, with one case of GBM in the last 15 years. This case series reviews the presentation, therapy and outcome of patients diagnosed with GBM at CHEO from October 2013 until June 2014.

Marina S. Yacob¹, Donna L. Johnston²

Affiliations: ¹B.Sc. Research Assistant, Division of Hematology Oncology, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada; ²MD, Pediatric Oncologist, Division of Hematology/Oncology, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada.

Corresponding Author: Donna L. Johnston, Division of Hematology/Oncology, Children's Hospital of Eastern Ontario 401 Smyth Road, Ottawa, ON, Canada K1H 8L1; Email: djohnston@cheo.on.ca

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CASE SERIES

Case 1

A male patient, age seven years and one month, was diagnosed with an exophytic pontine glioma. He presented with a one week history of vomiting, headache and double vision, difficulty turning his head from side to side, difficulty with eye movements to the lateral gaze bilaterally and ataxia. On physical examination he had a positive left facial palsy, and an abnormal forehead frown. An MRI scan showed a 3.6x4.2x1.7 cm pontine tumor exophytic into the fourth ventricle with compression of the basilar artery along the clivus. There was no evidence of spinal drop metastasis. The patient received radiation in a dose of 55.8 Gy in 31 fractions and temozolomide at 90 mg/m²/day during radiation therapy and then 200 mg/m²/day for five days every month. A three-month follow-up MRI scan found a decrease in size of the mass. A six-month follow-up MRI scan identified stability in the size of the pontine mass. Seven months after diagnosis the patient presented with vomiting, increased lethargy and ataxia for 24 hours. Brain CT scan showed an interval increase in size of the mass.

An MRI scan confirmed the increase in size of the lesion measuring 3.0x3.3x2.6 cm. There were new extensive signal changes in the posterior right inferior frontal lobe, the white matter in the peritrigonal regions, the right thalami in the posterior limb of the internal capsule extending to the right cerebral peduncle, and in the splenium of the corpus callosum on the right side. A spine MRI showed more nodular enhancements posteriorly at C5, and C7 to T1, that were suspicious for secondary lesions. A biopsy of the frontal lesion was undertaken and pathology showed glioblastoma multiforme. The patient was treated with radiation at a dose of 36 Gy in 20 fractions. He died nine months after his original diagnosis, and one month following recurrence at the age of seven years and 10 months.

Case 2

A female patient, aged 8.17 years, was diagnosed with an intramedullary spinal cord grade IV astrocytoma. She presented with difficulty extending her right 3rd, 4th and 5th digits that were in a constant flexed position inhibiting the use of her dominant hand. Her symptoms worsened within a week and she kept her thumb and index fingers flexed. She was also experiencing intermittent numbness and a pins and needles sensation of her right arm. She complained of intermittent neck, hand, elbow and shoulder pain. On physical exam her right upper limb showed significant muscle wasting involving the forearm and hand muscles, the scapula was lower on her right side associated with winging and she had a hypotonic right upper limb with hyporeflexia.

An MRI scan showed a 4.6x1.8x1.3 cm spinal intramedullary lesion from C4 to T1 (Figure 1A). There were no drop metastases, brain metastases or any evidence

of any syrinx. Lower limb somatosensory evoked potential demonstrated normal central conduction bilaterally. A C4 laminectomy was done with partial removal of the tumor mass as shown in Figure 1B. Pathology showed GBM. The patient then received radiation in a dose of 55.8 Gy in 31 fractions and temozolomide at 80 mg/m²/day during radiation followed by temozolomide at 130 mg/m²/day for five days and lomustine at 80 mg/m² for one day every 42 days.

Seven months after diagnosis, an MRI scan showed significant recurrence of her tumor locally measuring 1.0x0.9x4.1 cm and she died two months later at the age of 8 years and 11 months.

Case 3

A male patient, aged 13.5 years, presented with a one week history of left sided weakness and a three week history of lethargy, headaches, nausea and vomiting mostly in the morning. An MRI scan found a 5.2x4.7x5.4 cm right frontal enhancing lesion anterior to the central gyrus. Pathology showed glioblastoma multiforme with angiomatoid features and massive necrosis. An incomplete resection was performed with residual tumor being 2.5x2.0x4.0 cm. The patient then received radiation in a dose of 59.4 Gy in 33 fractions and temozolomide at 120 mg/m²/day during radiation therapy followed by Temozolomide at 220 mg/m²/day for five days and Lomustine at 120 mg/m² one day every 42 days. Nine months following diagnosis, the patient presented with nausea and vomiting and an MRI scan found an increase in the size of the lesion in the right frontal lobe which involved the corpus callosum measuring 3.7 x 7.5 x 5.5 cm. There was interval extension through to the body of the corpus callosum, the right basal ganglia, the right thalamus, the right frontoparietal subcortical white matter, and the posterior left frontal lobe. This recurrence was treated supportively with morphine, dexamethasone and physiotherapy. He died 10 months after his diagnosis and 1 month following recurrence at the age of 14 years and 4 months.

Case 4

A male patient, aged 5.75 years, presented with a one week history of intermittent headaches and nausea and a tonic clonic seizure lasting 10 minutes followed by left sided paralysis for 45 minutes. An MRI scan found a 7.0x4.0x4.0 cm lesion in the gray and white matter of the right temporal lobe. There was no hydrocephalus or other focal lesions and the spine was normal. An incomplete resection was carried out and he then received radiation in a dose of 59.4 Gy in 33 fractions and temozolomide at 90 mg/m²/day during radiation therapy followed by Temozolomide at 160 mg/m²/day for five days and Lomustine at 90 mg/m² for one day every 42 days.

Six months after initial diagnosis, the patient presented with diplopia and headaches. His CT showed a mass measuring 4.7x5.0 cm in the posterior right

temporal lobe with vasogenic edema, involving the right temporal, parietal and occipital lobes, with extension into the posterior limb of the internal capsule and lenticular nucleus in the right side. His recurrence was treated with steroids and morphine. He died one month after recurrence at the age of six years and four months.

Case 5

An 11.75 year old female patient was diagnosed with a secondary glioblastoma multiforme. Four years previously she was diagnosed with large B cell lymphoma with central nervous system involvement and received cranial radiation. One month prior to diagnosis of the GBM she presented with episodes of a flu-like illness, with headaches and vomiting mainly occurring in the morning. Her pediatrician noted the presence of papilloedema and a CT scan was done that showed a large lesion in the left parietal occipital lobes associated with edema and mass effect. An MRI scan of the brain demonstrated a large 3.2x3.3x2.0 cm heterogeneous enhancing mass in the left parietal lobe with extensive regional vasogenic edema (Figure 2A). She underwent a left parieto-occipital craniotomy and excision of the lesion (Figure 2B). She was treated with radiation in a dose of 54 Gy in 30 fractions and temozolomide at 120 mg/m²/day during radiation followed by temozolomide at 200 mg/m²/day for five days and lomustine at 120 mg/m² for one day every 42 days. She developed significant bone marrow suppression after one course of temozolomide and lomustine and so was treated with bevacizumab 350 mg IV q 2 weeks for 6 doses. The first dose of bevacizumab was given with 250 mg/m² of temozolomide.

Her tumor progressed nine months following diagnosis with multifocal bilateral lesions within the parietal and frontal lobes. She died 10 months after her GBM diagnosis and one month following her progression at the age of 12 years and 7 months.

DISCUSSION

Glioblastoma multiforme is the most common malignant primary brain tumor in adults, but is rare in children [1, 3–6]. During an eight month span at our medium-sized hospital there was a more than a ten-fold increase in incidence of GBM. The GBM occurred at a mean age of 9.25 years ($n = 5$), with the youngest being diagnosed at 5.75 years and the eldest being diagnosed at 13.50 years, which is comparable to literature, which showed the mean age of pediatric GBM to be between 8.8–12.7 years old [7]. Our male to female ratio was 3:2, similar to literature [8]. The incidence rate at our institution was 10.0%.

The main presenting symptoms included headaches (60%), vomiting (40%), nausea (40%) and limb weakness (40%). This is in accordance with literature, which notes common presenting symptoms of seizures, headaches, slowly progressive neurologic deficits, and symptoms



Figure 1: Magnetic resonance imaging of Case 2 showing: (A) Preoperative intramedullary lesion from C4 to T1, and (B) Postoperative imaging showing significant surgical resection.

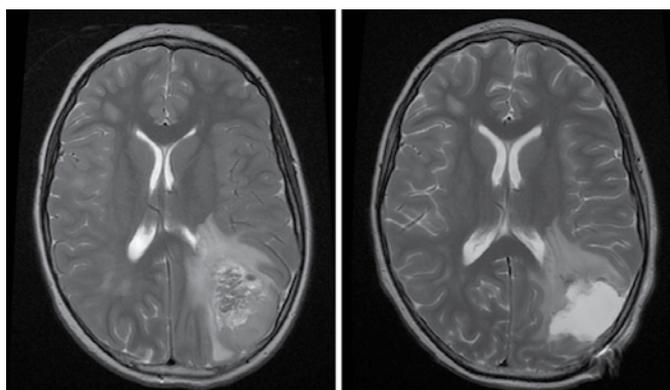


Figure 2: Magnetic resonance imaging of Case 5 showing: (A) Preoperative heterogeneous enhancing mass in the left parietal lobe with extensive regional vasogenic edema, and (B) Postoperative imaging showing significant surgical resection.

of increased intracranial pressure [9]. In children, the frontal lobe has been found to be the most frequent location for GBM (25–35% of cases) [7]. However, in this study only one patient had a lesion in the frontal lobe. Literature also shows that more than 90% of patients develop recurrence at the original tumor location and this was also demonstrated in our study in which all recurrences occurred locally, some with extension to other regions of the brain [10]. Finally, one pediatric GBM study found that infratentorial lesions were exclusively found in patients <11 years old, whereas supratentorial lesions were found in patients ≥11 years old [1]. In our study, both patients with infratentorial and spinal cord lesion were <11 years old (mean age=7.63 years old). The median survival for GBM is about 1 year, which is in accordance with our findings.

If possible, GBM should be treated with surgical removal of the lesion and adjuvant chemotherapy and radiotherapy [9]. One patient received a gross complete resection and survived 10.0 months. Three patients received a partial resection and survived an average of 8.67 months. Another patient received a surgical biopsy and survived 10.0 months. It is interesting that both patients that received either a gross complete resection or a surgical biopsy survived the same amount of time.

Literature suggests a better prognosis for complete resections [11], yet this was not found in this study. However, some literature suggests that no benefit in survival time is found with gross total resection and radiotherapy versus a partial resection [12].

Treatment included radiation therapy for all patients, varying from 55.8 Gy in 31 fractions (n=2) to 59.4 Gy in 33 fractions (n=2) for the patients with primary de novo GBM and a radiation dose of 54.0 in 30 fractions for the patient with secondary GBM. All of the patients were treated with chemotherapy including temozolomide during and after radiation, and 80% of the patients were also treated with lomustine. Additionally, the patient with secondary GBM was also treated with bevacizumab as she developed significant bone marrow suppression. Despite this therapy, no patients survived more than 10 months from diagnosis.

Recurrence is quite common in GBM patients with published recurrence rates of up to 90% [13]. All five patients in our series had a GBM recurrence. All of the patients were treated in a supportive manner, with morphine, and high dose steroids. The median interval from diagnosis to evidence of tumor recurrence was 7.6 months, which is considerably lower than some research, which suggests a 12-month median interval from diagnosis to evidence of tumor recurrence [14]. The median survival after GBM progression was 1.2 months.

CONCLUSION

In conclusion, the outcome of glioblastoma multiforme (GBM), remains poor, and the incidence of GBM increased at our institution. The majority of patients had primary GBM, with only one patient with secondary GBM. The median survival was 9.0 months after diagnosis indicating that this tumor remains a challenge to treat. Further investigation needs to go into the increased incidence of this tumor to see if it is a local or national occurrence, and this challenging tumor needs to have further therapeutic studies to try to improve the survival.

Author Contributions

Marina S. Yacob – Substantial contributions to conception and designs, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Donna L. Johnston – Substantial contributions to conception and designs, Acquisition of data, Analysis and interpretation of data, Revising the article critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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SUGGESTED READING

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