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Occurrence of Glioma in Pregnant Patients: An Institutional Case Series and Review of the Literature

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Abstract. *Background/Aim: Gliomas present a uniquely challenging clinical situation in the context of pregnancy, with no standard recommendations. This case series aimed to describe the treatment regimen and outcomes of five pregnant patients with gliomas. Patients and Methods: This is a retrospective study. A patient database from electronic medical records was evaluated to identify pregnant patients with gliomas treated at our institution between 2008-2018. Results: Five study patients who were pregnant with gliomas were identified. Of these, 4 were diagnosed during pregnancy, while 1 was diagnosed prior to her pregnancy. One patient had grade 2 astrocytoma, 1 had grade 3 anaplastic astrocytoma, and 3 had grade 4 glioblastomas (GBM). All patients received surgery, and one patient received radiation therapy without concurrent chemotherapy during her pregnancy. All delivered healthy babies. Three of the 5 patients remain alive, and 2 of the 5 were progression-free at the last follow-up. Conclusion: Treatment plans must be specifically tailored to the individual patient based on the glioma grade, the mother's desire to continue the pregnancy, and the risks of delaying treatment until after pregnancy. Additional studies need to be performed to definitively establish uniform guidelines for the treatment of pregnant patients with glioma.*

The management of glioma is dependent on the grade. Low-grade gliomas (Grade 2) can be monitored with surveillance imaging after a gross total resection. In some cases of high-risk grade 2 gliomas, treatment with concurrent chemotherapy with external beam radiation therapy (EBRT) is recommended. For high grade gliomas (grade 3 and 4), chemoradiation followed by chemotherapy is the standard of care. In select pregnant patients, surgery can be safely performed followed by focal cranial radiation with the use of a shielding device to minimize radiation exposure to the fetus (1, 2). It has also been observed that there is risk of progression from low grade to higher grade glioma during pregnancy (1). Chemotherapy is contraindicated due to its teratogenic effects during pregnancy. MRI can be safely performed on pregnant patients; the use of gadolinium based contrast is often determined by a case-by-case basis after completion of the first trimester due to unknown risk to the fetus (3).

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Key Words: Pregnancy, glioma, *IDH* mutated, radiation.

Patients and Methods

This was a retrospective case series review. Inclusion criteria included the diagnosis of glioma (from grade 2 to 4) during or prior to pregnancy. This yielded five patients from the electronic medical records at University of Texas Southwestern (UTSW). 3 patients had grade 4 glioblastomas (GBM), 1 patient had a grade 3 anaplastic astrocytoma diagnosed during pregnancy, and 1 patient was diagnosed with a grade 2 oligoastrocytoma prior to pregnancy. The courses of their pregnancies were tracked along with the treatment regimens as well as their survival outcomes. The use of contrast with their MRIs during pregnancy and outcomes of the newborns were also documented.

Results

Patient 1 was 32 years old when she initially presented with a seizure and was found to have a left frontal ring enhancing mass. She underwent a gross total resection (GTR) at 16 weeks gestation with pathology demonstrating the lesion to be a GBM (*IDH1* R132C mutated, *MGMT* unmethylated). She was followed by serial non-contrast MRIs for 6 months until delivery. After delivery she completed 6 weeks of

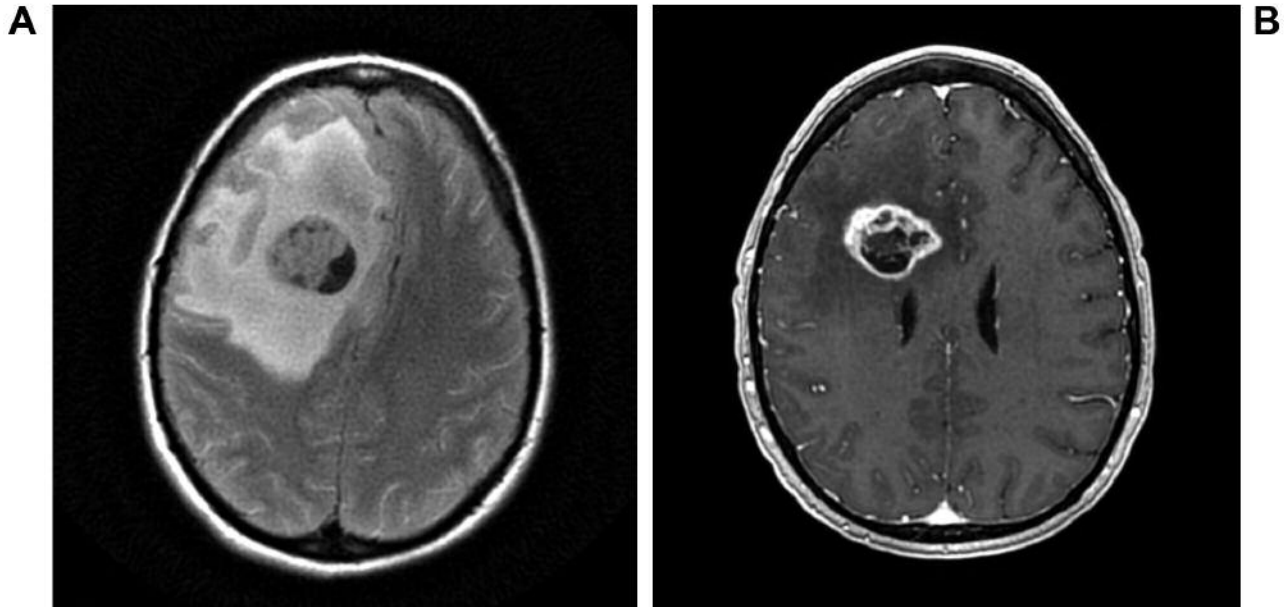

Figure 1. *MRI scans of patient 4 at initial presentation and radiographic progression. A: T2 image at initial encounter when patient presented in status epilepticus, initial images were taken without contrast. Pathology revealed to be GBM. B: T1-post contrast MRI obtained 4 months after initial presentation. Baseline MRI at 4 weeks after completion of 6-week course of concurrent radiation with TMZ; pathology confirmed radiation necrosis.*

concurrent EBRT with temozolomide (TMZ) chemotherapy and 11 cycles of monthly TMZ. She is currently on surveillance and remains alive and progression free up until her last follow up in October 2019 (96 months). Her child from this pregnancy had no reported birth defects and had a second pregnancy without complications.

Patient 2 was 27 years old at presentation with a new onset seizure at 17 weeks gestation. She was found to have a right frontal mass on brain MRI without contrast, and surgery was initially deferred for one month. Follow-up MRI with contrast showed progressive enhancement, and a GTR was performed at 25 weeks gestation with pathology showing the lesion to be a grade 3 anaplastic astrocytoma (*IDH1* R132H mutated). After resection, she deferred treatment until she underwent spontaneous vaginal delivery (SVD) 4.5 months after surgery. During that time, she was followed by contrasted MRI studies which showed an enlarging T2-FLAIR lesion near the resection cavity. After delivery she completed 6 weeks of EBRT with concurrent TMZ and subsequently 12 cycles of monthly TMZ. Patient has remained progression free at the last clinic visit before moving out of state. However, she unfortunately developed tumor progression and passed away approximately 55 months after diagnosis. Her child from this pregnancy had no birth defects.

Patient 3 was 32 years old when she initially presented with seizures at 9 weeks gestation. Brain MRI without contrast showing a left frontal mass. Subsequent brain MRI 1 month later showed further growth and GTR was achieved at 13 weeks gestation. Pathology showed grade 4 GBM (*IDH1* wild type, *MGMT* methylated). She was followed by contrast MRIs on a monthly basis during pregnancy after her first trimester. 4 months after GTR her GBM continued to progress and she received EBRT without concurrent TMZ during her third trimester. She delivered a healthy baby girl *via* C-section. She then completed 12 cycles of monthly TMZ. She underwent surveillance until she progressed in September 2019 (64 months) and was restarted on monthly TMZ. Her tumor subsequently stabilized and her child continues to thrive. She continues on monthly TMZ and has been stable as of her last follow up in March 2020.

Patient 4 was 38 years old when she presented status epilepticus at 27 weeks gestation and had emergent C-section without complications. She was noted to have a right frontal mass and underwent a subtotal resection (STR) 1 week postpartum. Pathology was consistent with a grade 4 GBM (*IDH1* wild type, *MGMT* unmethylated). One month after STR, she underwent concurrent EBRT with TMZ but developed symptoms concerning progression. She had a second resection (5 months from initial presentation) that demonstrated mostly radiation necrosis. Her neurologic symptoms improved and completed 6 cycles of monthly TMZ. However, she subsequently developed radiographic

Table I. *Characteristics of patients including age at presentation, gestational age of fetus, pathology of intracranial tumor at time of resection, and presence of MGMT methylation status. If IDH-R132H was negative by immune-histological stain, then IDH1 and IDH2 gene sequencing was performed.*

Case number	Age at presentation	Gestational age	Pathology	IDH mutation	MGMT status
Patient 1	32	16 weeks	GBM	IDH1-R132C	Unmethylated
Patient 2	27	15 weeks	Grade 3 astrocytoma	IDH1-R132H	NA
Patient 3	32	14 weeks	GBM	Wildtype	Methylated
Patient 4	38	17 weeks	GBM	Wildtype	Unmethylated
Patient 5	19	5 weeks	Grade 2 astrocytoma*	IDH1-R132G	NA

*At initial resection, later progressed to anaplastic astrocytoma.

Table II. *Treatment (extent of resection and radiation), survival, and outcomes.*

Case number	Extent of resection	Progression-free survival	Overall survival	Radiation during pregnancy	Outcome of infant
Patient 1	GTR	96 months	Alive	No	Healthy
Patient 2	GTR	Unknown	55 months	No	Healthy
Patient 3	GTR	64 months	Alive	Yes	Healthy
Patient 4	STR	11 months	19 months	No	Healthy
Patient 5	STR	40 months*	Alive	No	Healthy

*Progression-free survival measured from time of 2nd resection *vs*. initial resection.

progression necessitating dosage change in TMZ. There was continued disease progression and patient passed away approximately 19 months after initial diagnosis. Her child continues to do well at last contact (Figure 1A and B).

Patient 5 initially had a grade 2 astrocytoma status post resection at age 19 prior to her pregnancy and received surveillance MRIs with contrast every 3 months. She presented with a seizure at 5 weeks gestation and MRI without contrast showed a left temporal mass. STR was performed and pathology showed grade 2 oligoastrocytoma. Treatment was deferred and the patient was monitored with contrasted MRIs monthly starting in her second trimester. The patient delivered her child uneventfully and was continued on surveillance imaging every 2 months. She developed further progression of her tumor and underwent a second resection. Pathology confirmed the lesion to have progressed to a grade 3 anaplastic astrocytoma (*IDH1* R132G mutated). She completed a 6-week course of proton beam radiation with concurrent TMZ and subsequently completed 12 cycles TMZ in November 2017. She remains progression free on surveillance as of February 2020, and her child continues to do well. Table I summarizes the demographic profiles, tumor pathology and molecular findings, and Table II the treatment histories, progression-free and overall survival, and infant outcomes.

Discussion

All five study patients delivered healthy infants with no complications during or after birth. For those patients that required surgery during their pregnancies, GTRs were achieved. Patient 3 was able to successfully receive EBRT without concurrent TMZ during her pregnancy. Depending on the gestational age of the fetus, radiation could be given with shielding if absolutely necessary, but preferably deferred until after delivery if possible. Patients 2 and 3 were able to receive contrast MRIs during pregnancy after the second trimester with no detrimental effect to the fetuses. All patients were able to complete at least 6 cycles of adjuvant treatment with TMZ.

Two out of the five study patients who completed their course of TMZ are currently alive and progression-free, while two patients have deceased, and one is currently alive and progression-free on monthly TMZ.

Given the lack of definitive data to formulate standard treatment guidelines, developing individualized treatment plans is necessary for glioma patients who are pregnant. Clinical factors to consider when developing such treatment plans include tumor grade, extent of resection, and gestational status. Another very important factor to consider is the wishes of the pregnant patient with regards to her

baby. Several pregnant patients firmly expressed delivering a healthy baby as the primary priority, even at the cost of suboptimal treatment; while another study's patients clearly expressed that maximization of her tumor treatment was her first priority, even if that necessitated aborting the fetus. Such factors add to the complexity of developing the optimal treatment plan for this specific patient population. Quality of life concerns need to be addressed and managed. Having multidisciplinary discussions involving specialists for both the glioma and the pregnancy are critical to develop the optimum individualized treatment plans. Many of the treatment recommendations for these study patients were made in the weekly UTSW multidisciplinary Neuro-Oncology Tumor Board meetings.

Contrast MRIs may be performed after the first trimester if necessary. However, additional studies must be performed in order to more definitively determine the true risks of contrast MRIs in pregnancy. Although progression to higher grade can occur during pregnancy (1), in our case series only Patient 5 had progression from a low grade to high grade glioma after her delivery. This case series is the first to document *IDH* mutation and *MGMT* methylation status in pregnant patients with gliomas.

In this series, 3 of 5 tumor specimens were *IDH* mutated and 1 of 3 GBM specimens were *MGMT* methylated. Though a limited case series, patients with *IDH* mutation or *MGMT* methylated tumors had outcomes consistent with those reported in the literature (4, 5). Patient 1 with the *IDH1*-mutated GBM demonstrated survival over 8 years from her initial diagnosis, while Patient 4 with the *IDH* wild type and *MGMT* unmethylated GBM survived approximately 19 months from diagnosis, which is fairly typical for GBM patients with this molecular profile. Patient 3 with *MGMT* methylated GBM is alive nearly 6 years from initial diagnosis, which is consistent with outcomes of other *MGMT* methylated GBM patients. Patient 5 with the progressive grade 3 anaplastic astrocytoma that is *IDH1* mutated continues to remain alive over 7 years from initial diagnosis. Although there were too few patients in this cohort to make any definitive conclusions regarding any differences between the molecular profiles of gliomas in pregnant patients from non-pregnant glioma patients, obtaining such molecular information routinely may yield new insights in the future that may lead to more definitive treatment guidelines in this specific patient population.

Conclusion

The management of gliomas in pregnant patients is very complex and undefined due to the lack of definitive data regarding such issues as the safety of administering gadolinium contrast, administering brain radiation therapy, and the optimum time to initiate chemotherapy after delivery. Our experiences with this patient cohort suggest that for patients in their second trimester, MRIs with contrast can be safely obtained and that for high-grade gliomas in a pregnant patient, GTR or maximal safe resection can be achieved if necessary, particularly if the patient is symptomatic or the glioma is clearly progressing to a higher grade. Also, radiation therapy without concurrent chemotherapy can be safely administered with shielding of the fetus and taking other significant precautions. Following delivery, monthly TMZ can be administered per standard dosing as needed, although breastfeeding is not advised while taking TMZ. Although this was a retrospective case series with a limited sample size, it was observed that favorable clinical outcomes could be achieved. Obtaining molecular information about the gliomas regularly will likely be necessary to develop more definitive treatment guidelines for pregnant patients with gliomas. Multidisciplinary treatment discussions from the perspectives of glioma management as well as patient and fetal care are paramount to be able to achieve their optimum care without significant harm to mother and child. Given the rarity of newly diagnosed glioma in pregnant patients, creation of a national registry to track the outcomes of these patients would be potentially helpful. Such registries should include clinical, demographic, radiologic, and molecular data. With such detailed comprehensive data, guidelines for best management for this patient population can be identified and implemented.

Conflicts of Interest

None of the Authors have conflicts of interest to declare regarding this study.

Authors' Contribution

Dr. Pawan Singh gathered data and is the primary author of the article. Dr. Emmanuel Mantilla and Josie Sewell, FNP, provided edits and neuro-oncological expertise. Dr. Kimmo Hatanpaa assisted with provided edits and neuropathology expertise. Dr. Edward Pan is the main editor and team leader.

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