Advanced case of glioblastoma multiforme and pregnancy

An ethical dilemma

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ABSTRACT

الجليوبلاستوما أو الورم الأرومي المتعدد الأشكال من الخلايا الدبقية العصبية للمخ هو من اكثر الأورام الخبيثة انتشاراً. ولكنه نادراً ما يصاحبه حمل فوجود هذا الورم مع الحمل يمثل تحدياً ومخاطر للأم والجنين والأسرة والأطباء. وسوف نقوم بتقديم حالة غير اعتيادية لمريضة مصابة بهذا الورم وتم علاجها بجرعات قصوى من العلاج الكيماوي والإشعاعي وحدث حمل لهذه المريضة وتقدمت للعلاج عند الأسبوع الثامن عشر من الحمل وكان الإشراف الطبي وطرق المعالجة لهذا الحمل في منتهى الصعوبة من الناحية الطبية والمبادئ الاخلاقية. تم إجراء عملية قيصرية عند الأسبوع الثامن والعشرون وتمت العملية بنجاح برغم الحالة السيئة للمريضة. ولسوء الحظ فقد انتقلت المريضة إلى رحمة الله تعالى بعد أسبوعين من الجراحة. لذلك فقد استنتجنا أن هذا الورم (جليوبلاستوما أو الورم السرطاني بالمخ) المتكرر صعب العلاج أثناء الحمل ولكن نجاح هذا العلاج متوقف على تعاون الفريق الطبي المتكامل.

Glioblastoma multiforme (GBM) is the most common and malignant form of the glial tumors. Advanced and treated GBM is rarely associated with pregnancy for many reasons. Glioblastoma multiforme presenting during pregnancy carries unique challenges to the patient, baby, family, and health care providers. We describe an unusual case of advanced GBM that was treated with maximum doses of chemotherapy and radiations, and she became pregnant and presented at eighteenth weeks of gestation. Her medical management was associated with a significant ethical dilemma. We managed to deliver the baby safely through cesarean section at week 28 despite the critical condition of the mother. Unfortunately, the mother died 2 weeks post delivery. We concluded that although recurrent and treated GBM is rarely associated with pregnancy and carries dismal prognosis, but if it occurs, it can still be carried, and a multidisciplinary team work is the key for successful outcome.

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Glioblastoma multiforme (GBM) is the most common and malignant form of the glial tumors. The etiology of GBM is unknown in most cases. However, suggested causes included genetic susceptibility with single nucleotide polymorphisms in DNA repair genes, ionizing radiation, N-nitroso compounds exposure, head injury, occupational hazards, electromagnetic field exposure, possibly race, and cell-phone use (though it is still controversial).[1-3] Advanced and treated GBM is rarely associated with pregnancy for many reasons. Exposure to the standard therapy of glioblastoma usually adversely affects fertility.[4] Radiotherapy at a dose exceeding 45 Gy usually impairs the synthesis of gonadotropins, whereas the newer chemotherapy with alkylating agents, such as, temozolomide (TMZ) is associated with impaired ovarian function leading to premature menopause.[4,5] Glioblastoma multiforme presenting during pregnancy carries unique challenges to the patient, baby, family, and health care providers.[6] Additionally, evidence relating to timing of surgery and the use of radiotherapy and chemotherapy in pregnancy are still limited. The potential benefits to the mother must be balanced against the risks to the fetus.[7] We describe an unusual case of advanced GBM that was treated with maximum doses of chemotherapy and radiations, yet she managed to conceive. Her medical

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management was associated with a significant ethical dilemma, and we managed to deliver the baby safely through cesarean section at week 28 despite the critical condition of the mother. Unfortunately, the mother died 2 weeks post-delivery and the husband officially gave us the consent. We used the best available evidence in the literature to manage this patient and her baby.[4,7,8] The objective in presenting this particular case is to highlight on the possibility of delivering a baby of a pregnant patient with advanced GBM.

Case Report. A 36-year-old lady gravida 10, para 7, (G10P7+2) who is known to have advanced and non-operable right parital GBM was diagnosed with brain MRI (**Figure 1**) and brain biopsy (**Figures 2 & 3**) on October 2012. She received concurrent chemo-radiation with 60 Gyr /30 fraction treatment with oral temozolomide (TMZ) (75 mg/m^2 a total dose of 6 grams), and the treatment ended in December, 2012. This was followed by adjuvant TMZ for another 5 cycles (the total dose 8.750 grams) and the course was completed in May 2013. Three months after completing her adjuvant chemotherapy, she started to experience a deterioration in her vision that began on the left side then the right side followed. A follow-up brain MRI showed minimal interval changes in the surrounding edema with no significant tumor progression (**Figure** 4). She was seen by the ophthalmology and neurosurgery services, and they recommended a ventriculo-perotineum (VP) shunt, which was carried out on the 2nd of September 2013, and she was discharged from neurosurgery ward after that. On 15th of September 2013, she

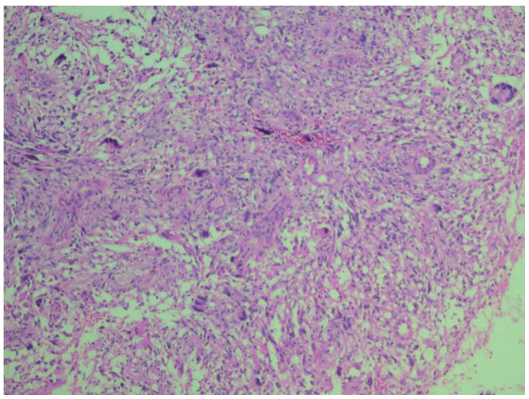

Figure 2 - Brain biopsy of right posterior parietal lobe of glioblastoma multiforme shows diffuse infiltration by a variably cellular glial tumors.

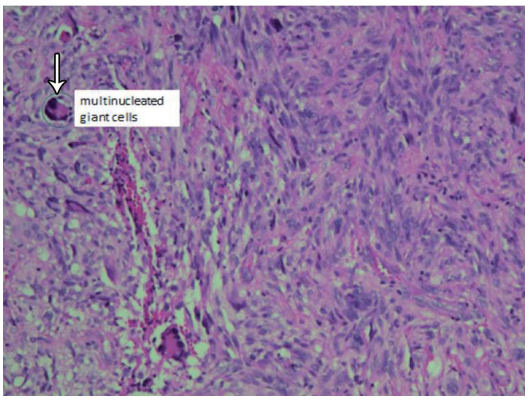

Figure 3 - Tumor cells of glioblastoma multiforme showed large pleomorphic nuclei with eosinophilic cytoplasmic processes and prominent multinucleated giant cell (arrow).

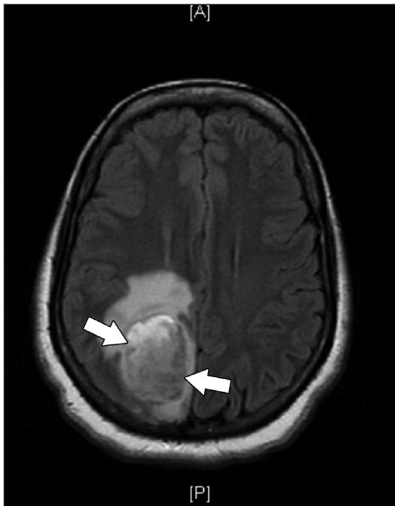

Figure 1 - Brain MRI shows large right posterior parietal lesion (ring enhancing lesion) (arrows).

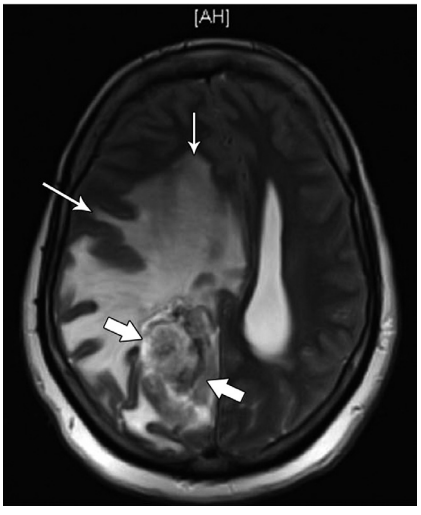

Figure 4 - Brain MRI showed minimal interval progression in the tumor component (wide arrows) and progression of the surrounding edema (narrow arrows).

presented to the emergency department with fever and a decreased level of consciousness. On examination, her BP was 114/86 mm Hg, pulse of 135 beats per minute, and body temperature 38.6 ºC. Her oxygen saturation on room air was 98% with normal glasgow coma scale (GCS), but neurologically she had left sided hemiplegia. Chest and cardiovascular examinations were unremarkable. Abdominal examination showed fullness in the lower abdomen. Pelvis ultra sound (US) revealed a viable fetus at 18 weeks of gestation with no obvious congenital anomaly.

Accordingly, she was hospitalized and treated with the appropriate antibiotics. Her husband and her family were informed with her pregnancy as well as the risk and anticipated complications that might happen during pregnancy. It was clearly stated by the patient and her husband that they would like to carry on with the current pregnancy. Initially, her family was in favor of terminating the pregnancy, but after the family counseling, their decision was to support the couples' choice. The case was referred to the high-risk pregnancy services and the religious committee; the situation was discussed in details, and the final decision was to carry on the pregnancy with closely monitoring the mother. Shortly after admission, she developed a decrease in her level of consciousness for which she was intubated, mechanically ventilated, and admitted in the ICU for further management. The repeated brain MRI in October 2013 showed significant brain edema with intra tumor bleeding (**Figure 5**). The neurosurgery recommendation was no surgical intervention, close observation, and conservative management. A follow-up US showed a normal female fetus with no congenital anomaly. The husband and the family were updated regarding the patient condition, and they still insisted to carry on with the pregnancy. In the ICU, she continued on mechanical ventilation and required tracheostomy; however, she remained in a coma with GCS of 3-4, but hemodynamically stable. A multidisciplinary meeting was held by the team, which included an ICU consultant, a medical oncologist, a high-risk obstetrician, and a neonatologist to discuss the situation of the patient and the expected outcome. Based on the limited evidence in the literature and the family's choice, the final plan was to: 1) Provide full support to the mother and render chemotherapy as directed by the medical oncology team. 2) Have an elective cesarean section (C/S) at the 28th week. 3) Have an emergency C/S at the 24th week if the mother got cardiac arrest. 4) No intervention before the 24th week.

At week 28, she had elective C/S, and the female baby was normal for gestational age with birth weight of 890 grams, Apgar scores were 8/1, 9/10; her post-delivery period was complicated with acute respiratory distress syndrome, sepsis, and jaundice, but ultimately, she recovered and was discharged home on stable condition. The mother was transferred back to the ICU, and 2 weeks later she was assessed for chemotherapy after a baseline brain MRI (**Figure 6**). She was started on palliative TMZ 5/28 day cycle, 2 days after she developed cardiac arrest, for which she was resuscitated but not revived, and pronounced dead on 18th of December 2013.

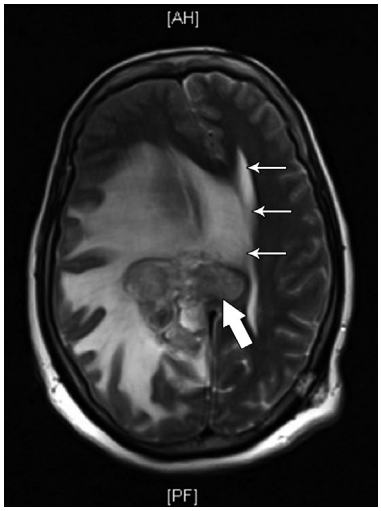

Figure 5 - Brain MRI showed significant increase in the size of the right posterior parietal glioblastoma multiforme (wide arrows) with increase in the right to left subfalcine (narrow arrow), and uncal herniation (not shown).

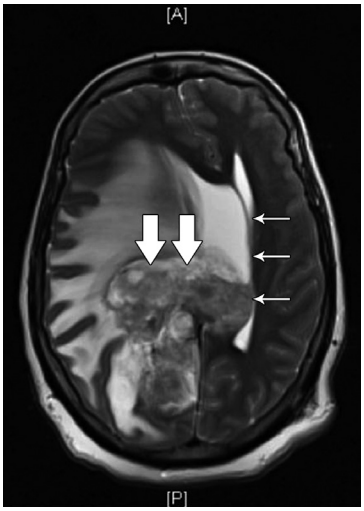

Figure 6 - Brain MRI (10 days post-partum); showed more necrotic component in the tumor (wide arrows), midline shift to the left (narrow arrow), and tonsillar herniation (not shown).

Discussion. Glioblastoma multiforme is the most aggressive primary brain tumor and usually carries a poor prognosis. Recurrent disease also has a worse outcome, and pregnancy makes the situation more challenging.[3] Glioblastoma multiforme in pregnancy can present with wide spectrum of symptoms and signs ranging from mild to severe. The symptoms can be generalized symptoms, such as headache, nausea and vomiting, syncope, and seizure disorders, or more common focal symptoms include visual, language, motor, and sensory disturbances. There is no clear guideline on how to manage a pregnant woman with GBM, and the management depends only on case reports and small series in the literature.[9,10] The administration of chemotherapy during pregnancy, especially during the first trimester is risky, and can induce harmful effects on both the mother and the fetus; in fact, the current recommendations are based on animal and epidemiological studies.[11] For the fetus, expected problems include congenital anomaly, organ toxicity, growth retardation, and developmental delay as well as potential carcinogenesis. The mother risk would include still birth, spontaneous abortion, and maternal sterility.[5-8] The common chemotherapy drugs used included TMZ, procarbazine, lomustine, and vincristine. Alkylating agents are known to cross the placenta and therefore, fetal toxicity can happen. The magnitude of the damage usually depends on the gestational age and the duration of exposure to these medications. Bevacizumab, which is an angiogenesis inhibitor is used as first-line therapy for recurrent GBM. It is considered pregnancy risk category C. Although radiotherapy is an important part of GBM treatment, it was not possible to give as she had her radiation in less than a year as directed by the radiation oncology team. Surgery is always an option for recurrent GBM and craniotomy can be safely performed during pregnancy, particularly early trimester. Following the result of pregnancy and knowing the patient and husband wishes, the risk of pregnancy versus benefit were fully explained to them by the managing team, high risk pregnancy services and the religious committee. In view of very limited data and only reported cases in the literature, we used the best available medical evidences to manage this patient. The multidisciplinary team which included the ICU consultant, medical oncologist, high risk obstetrician and neonatologist discussed with the family all the risks and benefits of the pregnancy, the natural history of the disease and the possible outcome as well as the available treatment options. It was decided to fully support the mother during her pregnancy and do elective Cesarean Section (C/S) on the week of 28th. However, in case she arrested between weeks 24th to 28th an emergency C/S will be immediately carried out, and no intervention to be carried out before the week 24th. Eventually, she underwent elective C/S on the week of 28th and delivered a normal female baby. Unfortunately, the mother died 2 weeks later due to cardiopulmonary arrest. The multidisciplinary management approach as well as the frequent family meetings were the key factors in managing this patient and her baby .[8,11]

In conclusion, advanced GBM in pregnancy is a medical and ethical dilemma and generally carries a variable prognosis. Continuous family counseling and multidisciplinary teamwork approach are the fundamental factors for a successful outcome.

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