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Case Report

Glioblastoma in pregnant patient with pathologic and exogenous sex hormone exposure and family history of high-grade glioma: A case report and review of the literature

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ABSTRACT

Background: Glioblastoma (GBM) incidence is higher in males, suggesting sex hormones may influence GBM tumorigenesis. Patients with GBM and altered sex hormone states could offer insight into a relationship between the two. Most GBMs arise sporadically and heritable genetic influence on GBM development is poorly understood, but reports describing familial GBM suggest genetic predispositions exist. However, no existing reports examine GBM development in context of both supraphysiologic sex hormone states and familial predisposition for GBM. We present a case of isocitrate dehydrogenase (IDH)-wild type GBM in a young pregnant female with polycystic ovary syndrome (PCOS), history of *in vitro* fertilization (IVF), and significant family history of GBM and further discuss how unique sex hormone states and genetics may affect GBM development or progression.

Case Description: A 35-year-old pregnant female with PCOS and recent history of IVF treatment and frozen embryo transfer presented with seizure and headache. Imaging revealed a right frontal brain mass. Molecular and histopathological analysis of the resected tumor supported a diagnosis of IDH-wild type GBM. The patient's family medical history was significant for GBM. Current literature indicates testosterone promotes GBM cell proliferation, while estrogen and progesterone effects vary with receptor subtype and hormone concentration, respectively.

Conclusion: Sex hormones and genetics likely exert influence on GBM development and progression that may compound with concurrence. Here, we describe a unique case of GBM in a young pregnant patient with a family history of glioma and atypical sex hormone exposure due to endocrine disorder and pregnancy assisted by exogenous IVF hormone administration.

Keywords: Familial glioma, Glioblastoma, *In vitro* fertilization, Polycystic ovary syndrome, Pregnancy

INTRODUCTION

A sexual dimorphism exists in glioblastoma (GBM) incidence, with men accounting for 1.6 times more diagnoses than women.[25] This discrepancy is not fully understood but highlights sex hormones as potential effectors of GBM development. Data supports that sex hormones

influence cancer cell biology. For example, testosterone promotes cancer cell development, while the effects of estrogen are largely dependent on type and level of estrogen receptor (ER) expression.[12,31] High doses of progesterone hinder GBM growth, while low doses may promote GBM growth.[3] Still, the full effect of each individual hormonal on GBM remains to be fully elucidated and there remains a particular lack of conclusive literature regarding GBM in the context of pathologic and supraphysiologic hormonal states, such as polycystic ovarian syndrome (PCOS) and *in vitro* fertilization (IVF) treatment protocols.

Genetic predisposition to GBM is rare and largely occurs in association with syndromes such as Li-Fraumeni and neurofibromatosis.[30,41] In a smaller subset of cases, there are apparent genetic effects on GBM incidence in the absence of these syndromes.[5] We present a case of GBM in a young pregnant woman with a family history of GBM and documented history of polycystic ovary syndrome (PCOS) and IVF treatment.

CASE DESCRIPTION

A 35-year-old pregnant female with past medical history of multiple miscarriages, PCOS, and IVF treatment presented to the emergency department following a generalized tonic-clonic seizure. On presentation, the patient was mildly post-ictal and reported headache and feeling lightheaded. The patient underwent frozen embryo transfer 9 weeks before presentation following a routine hormone protocol of daily oral and transdermal estradiol (E2), progesterone injections, and leuprorelin. At presentation, the patient remained on progesterone and enoxaparin injections in support of her pregnancy. She had no personal history of neurologic dysfunction, but family history was significant for GBM in her father and an unspecified brain tumor in a paternal aunt.

Computed tomography of the head demonstrated a 4 cm mass with significant vasogenic edema and minor mass effect but no midline herniation. The patient's obstetrician was informed and agreed to transfer to neurosurgery; a maternal fetal medicine consult approved starting the patient on levetiracetam. Subsequent noncontrast magnetic resonance imaging corroborated a 4.3 × 2.8 cm right frontal lobe mass with associated vasogenic edema, mass effect, and probable involvement of the right side of the corpus callosum without crossing the midline.

The patient underwent a right frontal craniotomy with maximal surgical debulking of the mass. She was discharged 4 days later and started Stupp protocol 36 days later following a dilation and curettage procedure for pregnancy termination. Final tumor pathology confirmed diagnosis of IDH-wild type GBM with genomic alterations including: disruption of SOX2, gain of function in estimated glomerular filtration rate (EGFR), homozygous loss of function in cyclin-dependent kinase inhibitor 2A and cyclin-dependent kinase inhibitor 2B (CDKN2B), and loss of function of phosphate and TENsin homolog deleted on chromosome 10 (PTEN).

DISCUSSION

This case provides a unique presentation of GBM in which several novel theories regarding GBM risk factors are represented. Here, we discuss the impact of sex hormones – through PCOS, pregnancy, and IVF – and heritable genetic risk on the development and growth of GBM. To the best of our knowledge, no reports of glioma in a pregnant woman following IVF for PCOS-related infertility exist in the current literature. This patient's family history of GBM makes this case particularly distinct.

Androgens

Testosterone and its metabolite dihydrotestosterone are well documented promoters of carcinogenesis and literature suggests this pro-cancer effect also applies to GBM. An initial animal study in 1970 showed that castrated rats had less induction of gliomas than non-castrated rats, implying androgen involvement in gliomagenesis.[14] More recently, Rodriguez-Lozano *et al*. found that human GBM cell lines exposed to high levels of testosterone increased proliferation, invasion, and migration [Figure 1]. Furthermore, they demonstrated the effects of testosterone on GBM are mediated by the androgen receptor (AR), as the proliferative effects of testosterone halted with the addition of an AR antagonist.[31] GBM may also upregulate ARs compared with the surrounding brain tissue. Yu *et al*. propose that AR signaling blocks downstream transforming growth factor beta (TGFβ) signaling, attenuating the pro-apoptotic effect exerted by TGFβ on male-patient derived GBM cells [Table 1].[45] These findings suggest that the discrepancy between testosterone levels in males and females could partly explain the increased incidence of GBM in men. Considering that young female patients account for a minority of GBM cases and PCOS is characterized – at least partly – by increased androgen secretion,[32] this case poses an interesting question of whether hyperandrogenemic conditions could be related to GBM development in certain patient populations.

Estrogens

A closer look at GBM incidence by age group reveals that the characteristic sexual dimorphism is greatest at the age-range of menarche, remains constant through adulthood, and decreases following menopause.[22] This timeline closely resembles the rise and fall of E2 levels throughout the female lifetime, suggesting a relationship between E2 and decreased GBM incidence in women. 2-Methoxy E2, a metabolite of E2, inhibited normal

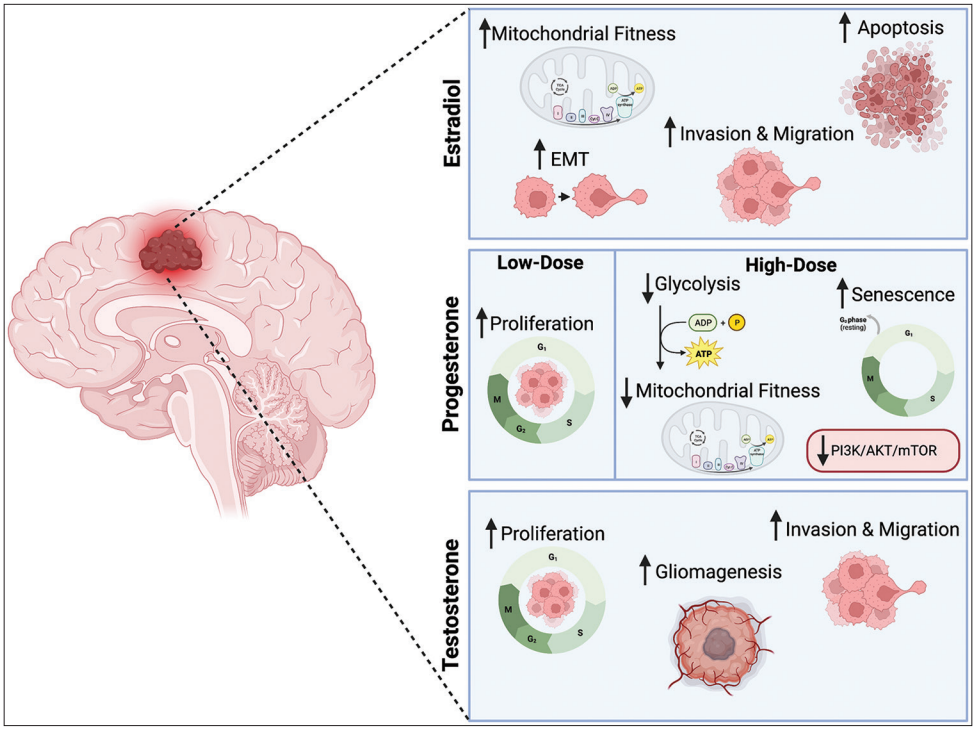

Figure 1: Summary of demonstrated hormone effects on glioblastoma.
EMT: Epithelial-mesenchymal transition, PI3K: Phosphatidylinositol 3-kinase, AKT: Protein kinase B, mTOR: Mammalian target of rapamycin, ADP: Adenosine diphosphate, ATP: Adenosine triphosphate, TCA cycle: Tricarboxylic acid cycle, CytC: Cytochrome C

Table 1: Summary of androgen and estrogen receptor effects.

Receptor type	Receptor effects and characteristics
Androgen receptors	↑ Expression in GBM ↓ Downstream effects of TGFβ, decreasing male GBM cell apoptosis
Estrogen receptor α	↑ GBM invasion
Estrogen receptor β	↓ Stemness and viability of glioma stem cells ↑ Mouse survival time in GBM ↓ Expression with increased astrocytoma grade
Estrogen receptor β1	Only estrogen receptor β-isoform with demonstrated tumor suppressive function in GBM
Estrogen receptor β5	↑ Expression with increased glioma grade

GBM: Glioblastoma, TGFβ: Transforming growth factor beta

and neoplastic glial cell proliferation and induced apoptosis of human GBM cells *in vitro*.[20] In contrast, E2 treatment of GBM cell lines induced proliferation by increasing genes related to mitochondrial fitness.[9] This inconsistency of findings prompts deeper exploration of E2's mechanistic intricacies.

A possible explanation for the conflicting results is that the ER type modulates the downstream effects of E2. Several studies demonstrate that estrogen's effects on GBM depend largely on which ER subtype, estrogen receptors alpha (ERα) or Estrogen receptor beta (ERβ), is targeted. Hernandez-Vega *et al.* found increased migration, invasion, and epithelial-mesenchymal transition markers in human-derived GBM cell lines exposed to E2, suggesting that E2 may promote GBM invasion. They further demonstrated that E2 promotes GBM invasion through ERα, but not ERBERB.[12] Instead, there is significant evidence that ERB is protective against GBM development and progression. ERB expression decreases with increasing astrocytoma grade.[6] Sareddy *et al.* demonstrated that ERB knockout in human derived GBM cell lines increased the stemness of glioma stem cells (GSC) and ERB agonists reduced GSC viability. They further showed that ERB receptor overexpression and ERB agonists prolong survival in GBM mouse models.[35] Furthermore, ERB activation may additionally sensitize GBM cells to the chemotherapeutic agent temozolomide (TMZ), as treatment with ERB agonists increased the survival time of tumor-bearing mice receiving TMZ.[46] Given these results, ERB agonists hold promise as a potential therapeutic strategy for GBM.[34]

These studies suggest a protective role of ERB, but it is worth noting that ERB has five isoforms (ERB1–ERB5),

each with documented distinct effects on different cancers. For example, ERB5 expression is correlated with better survival in breast cancer and non-small-cell lung cancer yet associated with poor prognosis in prostate cancer.[19,21,38] In the case of gliomas, ERB5 expression increases as glioma grade increases and influences mTOR signaling, cell growth, motility structures, and foci formation. Liu *et al*. found that ERB1 and ERB5 are the isoforms most expressed in human GBM, while ERB2 and ERB4 are present in low levels. Of these, only ERB1 demonstrated tumor suppressive function in GBM.[21] Thus, the proposed protective effects of ERB are likely attributable to the ERB1 isoform. The effects of estrogen and AR types are summarized in Table 1.

Although increased androgens are a hallmark of PCOS, there may also be disruptions of E2 and ERs. Specifically, ERα knockout mouse models are associated with the development of ovarian cysts and anovulation that mimics PCOS. ERB knockouts also experiencing decreased ovulation.[11,17,37] The relationship between PCOS and GBM remains largely undissected in the current literature, but it is possible that PCOS-associated dysregulation of ER signaling diminished the ability of E2 to exert any protective effects against GBM occurrence in this particular patient. Without specification of which ERs are present within a given tumor, it is difficult to predict how estrogen levels would affect GBM growth or development.

Progesterone

Evidence suggests that the effects of progesterone on GBM are concentration dependent. For example, Atif *et al*. found that high-dose progesterone decreased GBM growth, attenuated glycolysis, induced cellular senescence, inhibited the P13K/Akt/mTOR pathway, and improved survival, while lower dose progesterone had no impact on tumor size.[3] Increasing dose of progesterone also inhibited growth and downregulated tumor supportive mitochondrial proteins (mitochondrial ornithine aminotransferase and 60kDa heat shock protein) in GBM cell lines.[1] In contrast, Atif *et al*. found that low-dose progesterone (0.1, 1, and 5 μM) induced GBM proliferation that was blocked by a progesterone receptor (PR) antagonist.[4] Progesterone is additionally documented to attenuated the anti-tumor immune response through progesterone-induced blocking factor[10] and to activate cSrc through intracellular PR, thereby driving GBM progression.[8] PR antagonists also halted progesterone-induced GBM migration and invasion, further suggesting that hormonally targeting GBM may be a viable therapeutic strategy.[29] With such dichotomy of progesterone effects on GBM; further, research is necessary to establish upper and lower limits for the concentrations at which a GBM-blocking or promoting effect of progesterone can be consistently predicted. Such findings could elucidate any influence that this patient's progesterone treatment may have had on GBM development.

Pregnancy

One of the many changes that occur during gestation is a steady increase in E2 and progesterone, both of which peak in concentration during the third trimester.[39] Progesterone levels reach a lifetime high in the third trimester, but it is unclear whether these concentrations are ideal for mimicking the inhibition of GBM growth described in the preclinical literature.[1,3] An increased glioma growth rate and accelerated clinical deterioration is associated with pregnancy.[27,28] If the net effect of female hormones is indeed protective against GBM growth and development, this pregnancy-associated glioma growth may result from the many other growth factors released during pregnancy. For example, angiogenic factors such as vascular endothelial growth factor (VEGF) and placental growth factor support GBM growth and are increased during gestation.[16,24] Monoclonal antibodies against VEGF are associated with prolonged progression-free survival in GBM but is not recommended in pregnancy.[18]

Teratogenicity of cancer therapies is a significant barrier to GBM care during pregnancy, as surgery, anesthesia, radiation, and chemotherapy can all pose at least some level of risk to the fetus. The ethical dilemmas that arise when treating a pregnant patient with GBM are especially difficult to navigate given that the average survival time after GBM diagnosis exceeds the length of gestation by only a few months, often eliminating the option to postpone cancer treatment until after delivery.[43] In this case, the patient elected to terminate the pregnancy for these reasons.

Non-hormonal factors

While gonadal steroid hormones likely contribute to the sexual disparity in GBM incidence, other sex-specific differences in gene expression and immune function may also play a role. Sex differences in GBM incidence vary by cell type, with mesenchymal GBM cells displaying a larger sexual dimorphism than neural, proneural, or classical subsets of GBM. Greater inactivation of the tumor suppressor RB in males may be responsible for the augmented tumorigenesis and growth of mesenchymal GBM in male mouse models compared with their female counterparts.[40] Furthermore, females tend to respond better to standard therapy, demonstrating steadier declines in GBM growth velocity after TMZ treatment, and ultimately exhibiting longer survival times.[44] Yang *et al*. additionally demonstrated that net infiltration rates predicted survival time in females but not in males, and further identified a female-specific association between isocitrate dehydrogenase 1 (IDH1) mutation and longer survival.[44] In contrast, Schiffgens *et al*. found that IDH1 mutations predicted longer survival in males only.[36,44] Other identified predictors of survival included an associated between high expression of Wnt

receptor Frizzled-7 and poor survival in males, and an association between a hypermethylated MGMT promotor and longer survival in females.[36] Sex differences also exist in the expression of myeloid-derived suppressor cells (MDSC), which block the antitumor immune response and are increased in GBM. Monocytic MDSCs are elevated in male mouse models, while granulocytic MDSCs are expressed more abundantly in female mouse models. Bayik *et al*. found that chemotherapeutic targeting of monocytic MDSCs extended survival in male mice, while IL1 pathway inhibitors that inhibit granulocytic MDSC function extend survival in female mice.[7] Given the differential expression of potential therapeutic targets, increase consideration of sex-specific differences in therapeutic development may result in improved GBM survival in the future.

Heritable factors

Inheritance of GBM is uncommon and often associated with Li Fraumeni syndrome, neurofibromatosis, or Turcot syndrome.[13] However, reports exist of familial GBM in the absence of these syndromes.[2,23,33,42] A meta-analysis of three genome-wide association studies (GWAS) estimated a 25% and 26% heritability for glioma and GBM, respectively; yet, currently only an estimated 6% of genetic variance is explained by GWAS-identified glioma risk loci.[15] As such, a very small fraction of GBM heritability is understood. Genes associated with GBM in both males and females include those for solute carrier family 6, member 18, telomerase reverse transcriptase, CDKN2B, and strathmin 3.[26] Notable familial GBM cases include one reported by Sander *et al*., in which a brother and sister each acquired IDH-wild type multifocal GBM in the left parietotemporal lobe at the age of 63.[33] Mukherjee *et al*. sequenced DNA from GBMs of two siblings and their father with GBM diagnosed at ages 19, 6, and 38, respectively, to find they all shared mutations of platelet derived growth factor receptor-alpha and proto-oncogene H-Ras, and the two siblings shared a mutation of the SWItch/sucrose non-fermentable-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1) gene. They suggest that SMARCB1 predisposes to earlier GBM development.[23]

The genomic alterations identified in this case of GBM included disruption of SOX2, gain of function in EGFR, homozygous loss of function in CDKN2A and CDKN2B, and loss of function of PTEN. This analysis is notably limited by a lack of genetic characterization of the tumors from both the patient's father and paternal aunt. More reports detailing familial occurrences of GBM with DNA sequencing are needed to further elucidate the contributions of non-syndromic genetic heritability in GBM as genetic findings thus far are diverse and of limited relevance to this small subset of GBM.

CONCLUSION

This case describes a unique presentation of GBM in a young female patient with PCOS, history of IVF treatment, pregnancy, and significant family history of GBM and brain tumor. To the best of our knowledge, there are no previous reports of GBM presenting within this context. The existing literature poorly characterizes the relationship between these factors and further research is necessary to improve GBM survival and elucidate associations among GBM, genetics, biological sex differences, pathologic and supraphysiologic hormonal states, and pregnancy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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