Simultaneous Presentation of Glioblastoma Multiforme in Divorced Spouses

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Abstract
High-grade gliomas are the most common primary brain tumors in adults. However, with an incidence of 4/100,000 per year, glioblastoma multiforme is uncommon enough to make simultaneous presentation of identical tumors in husband and wife exceedingly rare. We report the fourth couple in the literature presenting with malignant astrocytomas concurrently. Despite being divorced and living apart for two decades, they presented on the same day, overhearing and recognizing each other’s voice in the emergency room. We include here the molecular characteristics of the tumors in both husband and wife, favoring the independent development of concurrent primary glioblastomas. Despite the number of conjugal presentations reported, genotoxicity and gliomagenesis may remain a completely independent event in spouses, dependent on endogenous factors damaging DNA. The slowly increasing incidence of gliomas, with nearly 100% correct nosologic recognition of this tumor entity, may lead to further recognition of independent but concurrent brain tumors in spouses.
Introduction

The incidence of glioblastoma multiforme (GBM) is just over 4/100,000 per year [1, 2] and appears to be slowly increasing [2–4]. We here present the fourth reported case of conjugal malignant glioma with synchronous presentation. Primary glioblastoma is suggested, and we include the molecular characteristics of tumors in both patients, who presented in the emergency room on the same day despite being divorced and estranged for 20 years. Both patients presented on January 9, 2017: one as a stroke alert and the other as a walk-in to the emergency department. It was noted by staff that the 2 patients had identical last names as their hospital beds were placed adjacent to each other. On the first evening of admission, patient 1’s son recognized patient 2 as his father, who had been married to his mother 20 years prior.

Case Reports

Patient 1

On January 9, 2017, a 65-year-old woman was brought to the emergency department as a stroke alert with acute onset aphasia, dysarthria, and subtle right-sided weakness. She had a past medical history of single seizure in 1995, hypothyroidism, essential hypertension, dyslipidemia, and type 2 diabetes mellitus. Examination revealed global aphasia, right facial droop, subtle right-sided pronator drift, and Babinski reflexes symmetrically. As shown in Figure 1, emergent CT brain with contrast revealed two mildly hyperdense, mildly enhancing lesions in the left parietal lobe with local sulcal effacement.

Patient 1 was born and raised in the Saskatoon area and worked as a receptionist at a local clinic. She smoked since the age of 17. She had no personal history of malignancy, had a first cousin with an unknown primary CNS neoplasm, and her father passed away from urothelial carcinoma that metastasized to his brain. Otherwise, a thorough exposure history including radiation, toxin, occupational, and infectious exposures revealed no further etiologic information.

She was admitted to hospital with plans for an MRI and EEG and was loaded with Dilantin. MRI revealed several mass-like T2-hyperintense and T1-hypointense regions

![Fig. 1. Patient 1's emergent CT shows noncontrast (left) and CT with contrast (right) showing two left parietal hyperdense, enhancing lesions.](image-url)
with cortical, subcortical, and callosal involvement. These lesions demonstrated some diffusion restriction and patchy contrast enhancement. EEG revealed continuous focal slowing in the left hemisphere, primarily in the left temporal region. CT chest, abdomen, and pelvis revealed no site of primary malignancy. A brain biopsy was performed on January 24, 2017. Pathologic evaluation revealed the features of GBM, IDH wild type (Fig. 2).

The patient was discharged from hospital as she had returned to her baseline with plans to follow up with oncology, receiving concurrent radiation and chemotherapy. She was readmitted to hospital on May 14, 2017, with progressive right-sided weakness and aphasia. For this, she was given dexamethasone and improved dramatically. She was discharged home on May 25, 2017, with plans for outpatient follow-up with Oncology. She ultimately passed away on March 16, 2018, a survival of 431 days.

**Patient 2**

Patient 2 also presented on January 9, 2017, as a 67-year-old man with a 2-week history of progressive right-arm numbness and left-arm and leg weakness. He had been on vacation in Arizona when he initially noted right-arm numbness. This sensation...
progressed over the following week, and he soon experienced left-arm and -leg weakness. On January 9, 2017, he was disoriented and confused. This prompted his current wife to fly home with him and present to the emergency department. He had a past medical history of a recent left humeral fracture secondary to a fall from a ladder, basal cell carcinoma resected in 2016, and essential hypertension. His examination revealed intact cognition, language, and cranial nerves. Significant global left-sided weakness was present in the upper and lower extremity, worse proximally in the upper extremity and distally in the lower. Reflexes were symmetrically brisk, and Babinski responses were extensor bilaterally.

An urgent CT scan is shown in Figure 3 and revealed features of multifocal glioma with enhancing lesions in the left cerebral hemisphere and right cerebellum. MRI of the brain revealed that these lesions were T2-hyperintense, T1-hypointense, and contrast-enhancing. MRI of the complete spine revealed extensive intraspinal dissemination, most notably in the proximal cervical cord extending to the fourth thoracic vertebral level but also involving the mid to distal thoracic cord, S1 nerve rootlet, and meninges.

Patient 2 was born near Prince Albert and raised in the Saskatoon area. He spent some of his career assisting on a dairy farm where he was exposed to multiple chemicals and pesticides. This job was concurrent with his time married to patient 1. He retired in 2009 and spent his winters in Arizona. His only past medical history of malignancy was basal cell carcinoma resected from his forehead in 2016. He had two healthy children with patient 1 and no family history of primary CNS neoplasms. There was no consanguinity between him and patient 1. Otherwise, a thorough exposure history revealed no concerning exposures in regard to radiation, toxins, or infectious etiologies.

His neurologic status deteriorated rapidly on his first day of admission, and he received dexamethasone as well as emergent radiation therapy. A brain biopsy Jan. 14, 2017, was nondiagnostic. Further investigations were negative, including CT of the chest, abdomen, and pelvis; CSF analyses; bone scan; serum protein electrophoresis; and HIV serology. A second brain biopsy on February 17, 2017, was again nondiagnostic. A third brain biopsy on March 31, 2017, pathologically established the diagnosis as GBM, with no mutations in IDH1, IDH2, nor H3F3A genes, and no significant methylation of the MGMT promoter gene (Fig. 2).

Throughout his stay in hospital, patient 2 deteriorated in his motor function, muscle tone, and cognition. He was transferred to the Palliative Care ward on April 11, 2017, for comfort care and passed away on June 2, 2017, a survival of 144 days.
Pathology

Both patients showed highly mitotic glioblastomas (Fig. 2), with a Ki67 labeling index of over 20%, glial fibrillary acidic protein positivity, little evidence of p53 mutation, and no IDH immunopositivity, suggesting overexpression of mutant protein. Immunohistochemical staining of both tumors and two age-matched and sex-matched control glioblastomas were done because of the potential role of cytomegalovirus (CMV) in gliomagenesis and progression [5–7]. No staining was seen that would suggest the presence of CMV protein in the tumors.

Discussion/Conclusion

GBM is the most common aggressive primary brain tumor in adults, accounting for 12–15% of all intracranial neoplasms. Of glial cell origin, GBMs arise from progenitor cells that outnumber neurons. They tend to occur in men more frequently than women and in higher socioeconomic groups [8], with a peak incidence between 45 and 70 years of age. Without treatment, the mean survival of patients in this age-group with GBM is 3 months [9]. With optimal treatment of combined resection, chemotherapy, and radiation, the mean survival is 12–15 months.

No specific risk factors have been explicitly implicated in the development of GBM, although risk factors for the development of cancer in general, including radiation exposure, chemicals, toxins, viruses, and genetic predispositions, have been extensively studied in this population. Although genetic anomalies have long been known to predispose individuals to the development of neoplasms, GBM has never been associated with such genetic mutations and syndromes. Exhaustive studies on electromagnetic fields, pesticides, solvents, and other chemicals have largely been inconclusive [3]. However, one study did suggest an association with exposure to carbon tetrachloride [10] and methylene chloride [11]. CMV may oncogenically promote GBM [5–7]. We found no immunostaining for CMV, and there has been no definitive evidence for CMV in gliomagenesis [10], although trials are underway [7]. The weak to absent associations with environmental factors argue for stochastic endogenous causes such as DNA oxidation, in explaining the progressive mutagenesis that occurs in glioblastoma: gliomas show a redox state that is tilted toward oxidation over reduction, with free radical production [12], known to cause DNA oxidative adducts that mispair to cause point mutation mutagenesis [13, 14]. Figure 2 illustrates why these two concurrent cases are not due to GBM overdiagnosis [4].

In our cases, there was no consanguinity between the ex-spouses. Furthermore, specimens from both biopsies were sent for molecular and genetic analyses with no genetic predilection identified. As certain viral infectious agents are also well known to be carcinogenic, extensive serum and cerebrospinal fluid analyses were completed with no infectious etiologic agent identified. Neither patient had a history significant exposure to radiation. The only possible etiologic agent identified was a historical occupational exposure to unidentified chemicals while patient 2 was working on a dairy farm for a brief period of time during his marriage to patient 1. Unfortunately, as this possible exposure occurred so remotely in the past, it is unclear what chemicals were used on the farm. Carbon tetrachloride, the only chemical with potential etiologic link to GBM in the literature, is not routinely used on dairy farms [10].

Primary glioblastoma refers to a tumor that appears de novo, whereas secondary glioblastoma denotes a WHO grade IV tumor arising from accumulating mutations in a lower grade tumor that has often been present for years [15]. Both cases herein have the clinical, histologic, and molecular features of primary glioblastoma (Fig. 2). Therefore, it is doubtful that the single seizure occurring 20 years ago was the harbinger of patient 1’s glioma.
Our couple is the fourth in the literature to present with synchronous occurrence of high-grade gliomas. Tupchong et al. [16] reported concurrent cases of gemistocytic astrocytomas in spouses, diagnosed within 16 months of each other. In 1986, Griffin et al. [17] described a case of simultaneous GBM in a married couple, presenting within an interval of 20 months. A third case of concomitant GBM in a husband and wife, presenting within 1 month of each other, was reported by Roviello et al. [18]. The couple reported here is the only one to present simultaneously as the patients arrived at hospital within 3 h of each other.

In conclusion, presentation of the same disease in a husband and wife may be either coincidental [19] or due to shared ecology and lifestyle. The increasing incidence of glioblastoma [2–4] still leaves conjugal presentation a rarity, but at \((4 \times 10^{-5})^2 = 1.6 \times 10^{-9}\) cases per year, the published frequency seen in the couple’s incidence is fully explained as merely random. In our cases, and the other three reported cases of synchronous development of gliomas in married couples, no etiologic agent was identified despite extensive investigation [16–18]. Thus, while the idea is tempting that gliomagenesis has a common origin in a married couple, it is likely independent in spouses. Nevertheless, it is important to document the occurrence of conjugal disease such as this to properly assess factors related to a shared environment in the etiology of cancer.

**Statement of Ethics**

Ethics approval was not required. Study approval statement was not required for this study in accordance with local/national guidelines. Written informed consent was obtained from surviving son/next-of-kin for publication of his parents’ details of their medical cases and images.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

The 2 authors contributed equally to this manuscript. C.M.F. wrote the draft and obtained patient data. R.N.A. finalized the manuscript text and figures and also submitted.

**Data Availability Statement**

Data underlying this study resides in the electronic medical records of the patients and in the pathologic archives at Royal University Hospital. The data are available for review. Conditions for accessing the data are compliance with the Health Information and Privacy Act. The data generated and analyzed are included in this article. Further inquiries can be directed to the corresponding author RNA.
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