Association of Traumatic Brain Injury and Glioblastoma Multiforme: A Case Series

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ABSTRACT Glioblastoma multiforme (GBM) is an aggressive variant of central nervous system gliomas that carries a dismal prognosis. Although GBM is the most frequently occurring and malignant type of glioma accounting for more than 60% of all brain tumors in adults, its overall incidence is rare, occurring at a rate of 3.21 per 100,000 persons. Little is known about the etiology of GBM, but one proposed theory is that GBM pathogenesis may be linked to a chronic inflammatory course initiated by traumatic injury to the brain. Limited case reports have suggested an association between GBMs and traumatic brain injury (TBI), but larger case–control and epidemiologic studies have been inconclusive. We present three service members (two active duty and one retired) who developed GBM near the original site of prior head trauma. Each service member's military occupation was in the special operations community and shared a common theme of TBI following head trauma/injury. The current research on the association between TBI and GBM is limited and conflicting, predominantly due to the low incidence of the disease in the general population. Evidence has indicated that TBI should be considered a chronic disease with long-term health impacts, including long-term disability, dementia, epilepsy, mental health conditions, and cardiovascular diseases. With the addition of our patients, as well as a recently published study proposing a molecular association between trauma and GBM, further research is needed to better understand the potential relationship.

INTRODUCTION

Glioblastoma multiforme (GBM) is an aggressive variant of central nervous system gliomas that carries a dismal prognosis with a median survival of approximately 14 to 15 months from diagnosis.[1] Although GBM is the most frequently occurring and malignant type of glioma accounting for more than 60% of all brain tumors in adults, its overall incidence is rare, occurring at a rate of 3.21 per 100,000 persons.[1] The peak incidence arises in persons aged 55 to 60 years, but it can occur at any age.[2] The incidence of GBM is higher in men compared to women.[3] Modern therapies have allowed for a modest increase in average survival time, but GBM remains a terminal diagnosis with poor outcomes. Little is known about the etiology of GBM. High doses of ionizing radiation have been identified as a risk factor.[1] Conclusive associations with environmental risk factors such as diet, smoking, pesticide exposure, cell phones, and electromagnetic fields have not been shown.[1] Gliomas have been found to run in families, but the susceptible gene or shared environmental risk has yet to be identified.[4] Recent investigations indicate tissue injury and inflammation as a possible pathophysiologic explanation for the development of GBM.[5,6] Additional research is required to provide further insights into possible intrinsic and environmental risk factors that contribute to the development of the disease.

The formation of GBM has been documented in brain areas that were previously affected by injury to brain tissue.[2] Chronic inflammation is known to be associated with malignancies such as hepatocellular carcinoma, pancreatic cancer, and colon cancer.[7] Similarly, it has been proposed that the development of GBM may be in part linked to a chronic inflammatory course initiated by traumatic injury to the brain.[2,8] Several epidemiological studies have investigated the relationship between GBM and prior traumatic brain injury (TBI) with varying results.[8,9,10]

We present three service members (two active duty and one retired) who developed GBM near the original site of prior head trauma. Each service member's military occupation was in the special operations community. Traumatic brain injury has been common in combat veterans since 2001 and has an estimated prevalence of 25%. Traumatic brain injury risk is particularly high among special operations forces.[11,12] Given the high rates of TBI in special operations forces and the potential association with subsequent GBM, we present a series of three service members who developed GBM near the site of prior head trauma.

CASE PRESENTATIONS

Patient 1

Patient 1 is a 44-year-old male who initially presented with unwitnessed syncope after being found unconscious and unarousable in his kitchen by his wife. He would later recall

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preceding symptoms of lightheadedness and "tunnel vision." In the emergency room (ER), he reported only a mild, right-sided headache. A non-contrast head and neck computed tomography (CT) was normal, and he was discharged home with a diagnosis of vasovagal syncope. Two weeks later, he presented to the ER following another episode of syncope, followed by witnessed seizure-like activity described as generalized tonic/clonic movements involving the periphery of the upper extremities and tongue biting. Following the seizure-like activity, he was postictal for 30 minutes. Magnetic resonance imaging (MRI) of the brain revealed a left posterior frontal lobe lesion as well as T2 and T2-FLAIR (fluid-attenuated inversion recovery) hyperintense, non-enhancing lesions in the left frontal lobe deep white matter and right posterior frontal lobe cortical/subcortical parenchyma. He continued to have seizure events despite the initiation of antiepileptics. Repeat MRI brain (Fig. 1) showed multifocal areas of signal abnormality within the bilateral frontal lobe with tumor hemorrhage of the left superior frontal lesion. He subsequently underwent a craniotomy with subtotal resection. Surgical pathology demonstrated a WHO grade IV isocitrate dehydrogenase wild-type GBM. The patient completed chemoradiation with temozolomide and transitioned to maintenance temozolomide. He continued to exhibit clinical disease progression characterized by right-sided hemiparesis and aphasia despite multiple lines of treatment to include bevacizumab, lomustine, carboplatin + irinotecan, cyclophosphamide, and etoposide. He died a year and a half following his initial diagnosis.

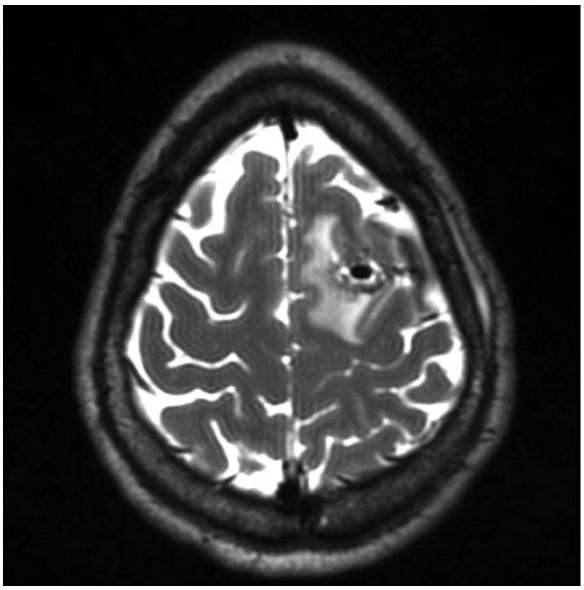

FIGURE 1. T2 MRI brain of patient 1.

A review of the patient's history was notable for multiple instances of head injury and trauma (Table I). He never had loss of consciousness with these events but recalled feeling "dazed" or "seeing stars." His most significant head trauma occurred as a blast pressure wave when a grenade was dropped off a roof, landing 6 feet away from him. He was knocked back, developed a severe headache, and felt dazed but was able to continue his mission.

Patient 2

Patient 2 is a 59-year-old male with a past medical history of well-controlled type II diabetes mellitus, obstructive sleep apnea on continuous positive airway pressure, and migraines who experienced acute onset dizziness and fall while at work. He was taken to the ER where a head CT revealed a large right brain mass. A subsequent brain MRI (Fig. 2) revealed a $4.2 \times 2.5 \times 2.1$ cm enhancing mass in the right frontoparietal cingulate gyrus resulting in a slight

TABLE I. Summary of Head Injuries of Patient 1

Year	Mechanism of injury (e.g., fall, fight, Motor Vehicle Accident (MVA), and blast)	Loss of consciousness/alteration of consciousness "dazed/confused"	Symptoms after the event
2000	Parachute, landing	Dazed for couple of minutes	Headache for a week Nausea for a day
2004	Parachute opening, whiplash	Seeing stars, tunnel vision	Headache for 2 days
2004	Rocket blast	Confused after multiple shots	Inability to think for a day
2005	Failed internal breach, blast	Dazed	Nausea for a couple of days Headache for a week
2005	Improvised explosive device (IED)	Dazed	Confusion
2005	Small-boat open-water transit in rough seas	Seeing stars	Weak afterward
2007	0.50 cal shooting overhead within 3 feet during troops in contact (TIC)	Dazed	Inability to think for a couple of days
2008	Hard fall on patrol	Dazed, confused	Nausea and confusion
2009	Combatant training, fight	Almost knocked out	Nausea and headache for a week
2013	Grenade dropped within 6 feet, blast	Dazed, confused, slow to react	Nausea for 1 week, ears ringing/headache 3 weeks
2017	Breacher training, failed breach, blast	Dazed	Nausea for 2 days
2017	Combatants training, fight	Dazed	Seeing stars, nausea 1 day

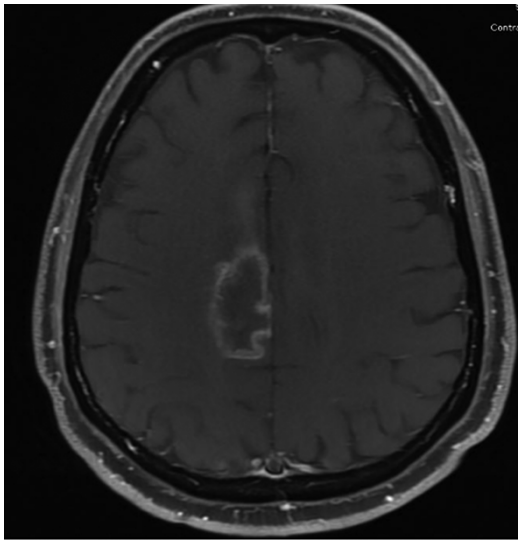

FIGURE 2. T2 MRI brain of patient 2.

midline shift. Additional findings were notable for enhancement involving the left cerebral hemisphere white matter. A biopsy was performed, which confirmed a WHO grade IV, (6)-methylguanine DNA methyltransferase unmethylated GBM. The patient received chemoradiation with temozolomide as part of standard therapy for GBM. The treatment course was complicated by the onset of left hemiparesis that was attributed to radiation-induced brain edema. Left hemiparesis improved with systemic corticosteroids and bevacizumab. He was then transitioned to maintenance temozolomide. The patient continued to exhibit disease progression, manifesting as a recurrence and gradual worsening of left hemiparesis.

Patient 2 served in the military for over 20 years in the special operations community. There are no documented head traumas, but his occupational exposures included parachuting, small-boat operations, and blast exposures similar to those of patient 1.

Patient 3

Patient 3 is a 40-year-old male with no significant past medical history who presented to the ER with a 1-week history of severe, unrelenting headache in the absence of other neurologic findings. He underwent a non-contrast head CT with findings of an approximate $3 \times 2.5 \times 2.7$ cm mass-like density in the right parietal lobe and associate vasogenic edema. A brain MRI was obtained with re-demonstration of a parietal mass along with additional findings of lesions in the left thalamus, occipital lobe, and right thalamus (Fig. 3). Given the location and extent of disease, the patient was deemed a candidate for surgical resection. He underwent biopsy, which revealed a WHO grade IV isocitrate dehydrogenase wild-type GBM. He was initiated on chemoradiation with temozolomide

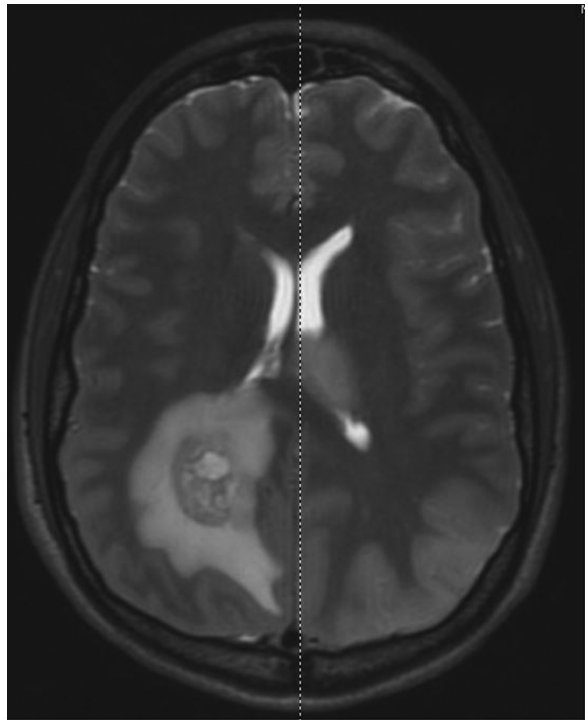

FIGURE 3. T2 MRI of patient 3.

but died from complications following a seizure shortly thereafter.

Patient 3 also served in the special operations community with exposures similar those of patients 1 and 2. Additionally, he suffered at least two documented traumas. The first in 2017 was a bad parachute landing resulting in multiple broken bones. The second, occurring in 2020, was consisted of multiple high-speed projectile injuries including shrapnel to the head.

DISCUSSION

We present three service members who were diagnosed with GBM. In two of the cases, the patients were significantly younger than the median age of diagnosis of 55 to 60 years.[2] They did not have any suspected risk factors for GBM to include a history of ionizing radiation or a hereditable condition such as Li-Fraumeni syndrome and Lynch syndrome.[8] Our patients did share a common theme of TBI following head trauma/injury.

There are case reports (in addition to our own series) that present a connection between TBI and tumorigenesis leading to GBM.[8,10,13,14] In one prior case report and review of the literature, Zhao et al. proposed the following criteria to suggest a causal relationship:

1. The injury must be severe enough to cause a tissue repair process to commence.
2. The area of the traumatic injury should correspond directly with the location of the subsequent GBM.

3. There should be a gap of at least 1 year between the injury to the brain and the appearance of the tumor. A longer latent period is considered to be a stronger evidence of a causal relationship.[10]

Several small case–control studies were published, which yielded conflicting results. Case–control studies by Hochberg et al. ($n = 160$) and Hu et al. ($n = 218$) found a positive association, an absolute risk ratio of 10.6 and an odds ratio of 4.09 (95% CI, 2.51–10.31), respectively, whereas Zampieri et al. ($n = 109$) found no significant association, odds ratio of 0.7 (95% CI, 0.3–1.40).[15–17] Similarly, several large-scale epidemiologic studies have also attempted to better characterize a potential relationship between TBI and GBM with varied results.[18] These studies are difficult to interpret owing to the heterogeneity of the study designs. As a result, a definitive link between head trauma and increased risk of GBM has not been shown.

More recently, Richards et al. published a study examining the genetic composition of GBMs in 26 patients. Their analysis of more than 69,000 glioblastoma stem cells found transcriptional heterogeneity that could not be fully explained by DNA somatic alterations and two cellular states reminiscent of normal neural development and inflammatory wound response were seen, suggesting GBMs develop in part because of wound healing.[6]

CONCLUSION

Glioblastoma multiforme is the most common primary brain malignancy in adults but rare, overall occurring with an incidence of 3.21 diagnoses per 100,000 persons. Glioblastoma multiformes are aggressive cancers with an average survival of 14 to 16 months from diagnosis. Limited case reports have suggested an association between GBMs and TBI, but larger case–control and epidemiologic studies have been inconclusive. With increased attention on the association between TBI and brain health, as well as recent studies proposing a molecular association between trauma and GBM, further research is needed to better understand the relationship.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY

None declared.

CLINICAL TRIAL REGISTRATION

None declared.

INSTITUTIONAL REVIEW BOARD (HUMAN SUBJECTS)

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INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)

Not applicable.

INSTITUTIONAL CLEARANCE

Institutional clearance approved.

INDIVIDUAL AUTHOR CONTRIBUTION STATEMENT

J.A., E.F., I.J.S., and M.D. all wrote, reviewed, and edited the manuscript. All authors read and approved the final manuscript.

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