CASE REPORT

Unusual Presentation of Stroke-like Symptoms Due to Diffuse Infiltrating Glioma with Primary Glioblastoma

Molly Farrell, Brent Alford

Department of Surgery, University of North Texas Health Science Center, Texas College of Osteopathic Medicine, Fort Worth Brain and Spine Institute, 3500 Camp Bowie Boulevard, Fort Worth, Texas 76107, United States

ABSTRACT

Gliomatosis cerebri (GC) is a rare glioma that has poor prognosis and a non-specific clinical presentation. Under the latest World Health Organization classification, GC is not its own class of tumor, due to lack of genotypic differentiation from other gliomas, but a unique growth pattern including more than three cerebral lobes, typically bilateral and including the infratentorial space. The current case study illustrates an 81-year-old male after a stroke-like presentation due to a diffuse infiltrating glioma, consistent with previously defined GC, and a concurrent primary glioblastoma. GC has no current standard of care and the etiology of the distinctive growth pattern remains unknown.

Key words: Diffuse infiltrating glioma, glioblastoma, gliomatosis cerebri, stroke-like presentation

INTRODUCTION

Gliomatosis cerebri (GC) is a rare, previously separate, classification of glioma with poor prognosis and without specific clinical presentation. It is more common in males with an overall age-adjusted incidence rate of 0.1/1,000,000 and with a median overall survival of 9 months.[1] GC is defined as a diffuse infiltration of the tumor into more than three lobes of the cerebrum, often bilaterally and in the infratentorial space. GC has been removed from the World Health Organization (WHO) classifications of central nervous system (CNS) tumors due to the lack of genotypic differentiation from other gliomas.[2] The tumor can present with a wide variety of neurological symptoms due to the infiltrative and diffuse extent of the tumor. Such neurological deficits can present as weakness, numbness, loss of vision, executive dysfunction, fatigue, memory difficulties, or seizures.[3,4] It is common for patients to present with headaches, papilledema, and other symptoms of increased intracranial pressure.[3]

The WHO grading system of gliomas is based on histology to define biological behavior and guide clinical therapeutic interventions.[5] It is noted in the WHO 2016 classification that diffuses infiltration of gliomas, previously known as GC, has an unknown cause for such extensive invasion of these tumors.[6] Therefore, with the uniquely extensive phenotypic growth pattern, diffusely infiltrative gliomas need further studies to determine biologic drive of growth and help guide treatment. The current case study is a description of a patient with a stroke-like presentation, likely due to the diffuse infiltrating glioma, and adds to the literature of this rare tumor growth pattern.

CASE REPORT

An 81-year-old Brazilian male, who is a retired machinist, presented to the neurosurgical clinic for evaluation after receiving abnormal imaging results. The patient's symptoms began 2 months prior when he "passed out" in his home in Brazil. At that time, the patient reported right-sided weakness and speech difficulty consistent with stroke. He was transported to the hospital by emergency medical services, during which he had witnessed seizures *en route*. When the patient arrived at the hospital in Brazil, he was diagnosed as having a stroke though it is unclear what imaging showed

Address for correspondence:
Molly Farrell, Department of Surgery, University of North Texas Health Science Center, Texas College of Osteopathic Medicine, Fort Worth, Texas 76107, United States. E-mail: Molly.Farrell@my.unthsc.edu

at this time. He was hospitalized for 3 weeks due to the development of aspiration pneumonia and renal failure. On recovery from his hospital stay, the patient traveled to the United States. On arrival, the patient presented to a neurologist for stroke follow-up. At that time, magnetic resonance imaging (MRI) of the brain without contrast was completed which showed extensive leukopathology, likely GC, and a cystic lesion in the right hemisphere suspicious for a tumor.

The patient was then referred for neurosurgical evaluation. On physical examination, the patient was awake, alert, and oriented to person, place, and time. The patient's speech was relatively fluent with some difficulty with complex repetition and mild memory and concentration difficulties. His pupils were 2 mm × 2 mm bilaterally and reactive to light. Extraocular movements were intact with no nystagmus or diplopia. The patient's face was symmetric without weakness and tongue was midline. There was subtle right-sided pronator drift but with close to full strength throughout his right upper and lower extremities and full strength of his left upper and lower extremities. There was no clear Hoffmann's or clonus. The patient had minimal dysmetria without tremor.

The patient received a pre-operative MRI of his brain with and without contrast that identified an enhancing 15 × 18 × 18 mm lesion in the lateral right parietal lobe, likely involving the right supramarginal gyrus. This lesion was likely an area of dedifferentiation tumor/necrosis [Figures 1 and 2]. This presented also with mild mass effect on the left cerebral hemispheres with minimal 1–2 mm midline shift. There was also diffusely abnormal appearance of the brain with extensive multifocal areas of irregular thickened fluid-attenuated inversion recovery signal hyperintensity throughout the cerebral hemispheres and brainstem, but not in the right parietal lobe. The appearance was suggestive of diffuse infiltrative glioma [Figure 3]. Computerized tomography (CT) scans of the thorax, abdomen, and pelvis were performed to rule out metastatic disease. Scans showed an enlarged prostate gland, a few small pulmonary non-specific nodules, and 1 cm indeterminate left renal lesion. Further, imaging is recommended for follow-up of CT scan findings, but no metastatic disease was suspected at the time. Of note, there is no evidence of a previous stroke on the patient's imaging. Without indicative imaging of a previous stroke process and with the patient's rapid improvement in strength and speech, the left hemispheric dysfunction experienced by the patient is likely due to his diffuse infiltrating left hemispheric tumor.

The patient underwent a right parietal craniotomy with resection of the right parietal lesion. Intraoperatively, the lesion was posterior to the primary sensory cortex and

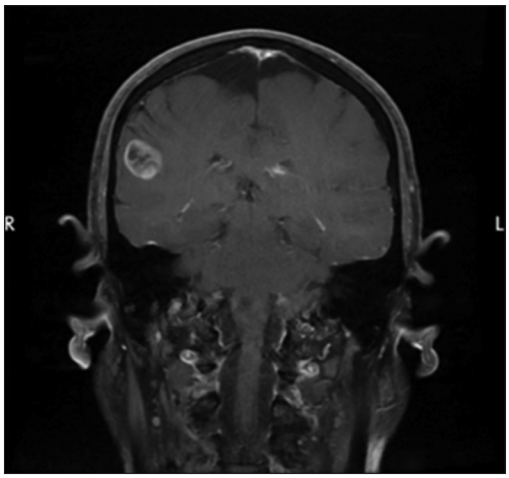

Figure 2: Magnetic resonance imaging brain T1 with and without contrast, coronal section of the brain showing a ring enhancing lesion in the right parietal lobe

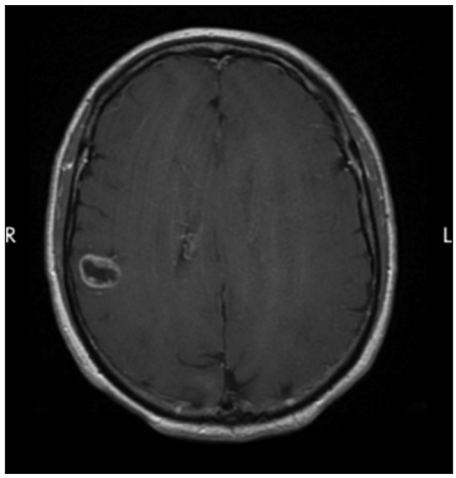

Figure 1: Magnetic resonance imaging brain T1 with and without contrast, horizontal section of the brain showing a ring-enhancing lesion in the right parietal lobe

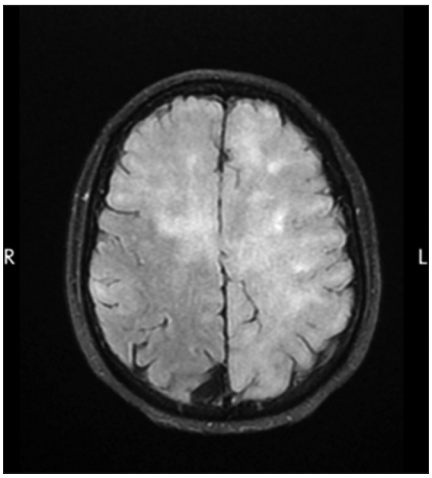

Figure 3: Fluid-attenuated inversion recovery magnetic resonance imaging brain T2 with and without contrast, horizontal section showing diffusely abnormal multifocal areas of irregular thickened signal hyperintensity

superior to the Sylvian fissure. The resected tumor tissue grossly measured 37 mm × 10 mm. The patient had an uneventful recovery with no neurological deficits and was discharged on post-operative day 2. The pathology report indicated the right parietal lesion as glioblastoma (GBM), isocitrate dehydrogenase (IDH)-wild type, non-mutated. The patient was referred to neurological oncology for further treatment recommendation.

DISCUSSION

By the WHO 2007 grading system, infiltrative gliomas with cytological atypia are Grade II (diffuse astrocytoma). Tumors that have additional anaplasia and mitotic activity are Grade III tumors (anaplastic astrocytoma). Finally, those tumors with additional microvascular proliferation and/or necrosis are high grade, Grade IV, gliomas (GBMs).[5] In the 2016 WHO classification, diffusely infiltrating gliomas, consistent with previously classified GC, are classified on phenotype and genotype and can be Grades II, III, or IV.[6] CT imaging is often not sensitive enough to detect the degree of disease present of GC. MRI can provide further insight into the degree of diffusion and GC type. GC type 1 (more common) is characterized by diffuse tumor without a localized solid tumor mass, while GC type 2 includes an obvious solid mass with the diffuse infiltration.[7] GC differentiates from multifocal gliomas due to the contiguous expansive infiltration without clear distinction between normal and diseased tissue.[4] The patient presented with a localized GBM in the right parietal lobe in addition to the diffusely infiltrative glioma throughout the cerebral hemispheres and brainstem with sparing to the right parietal lobe.

GBM accounts for 14.7% of all primary CNS neoplasms and is the most common type of glioma, 56.6% of all gliomas.[8] GBM has the highest occurrence for malignant tumors of the CNS, age-adjusted incidence rate of 3.21/100,000 populations. This incidence increases with age resulting in individuals ages 75–84 years having the highest incidence, 15.13/100,000 population.[8] GBM does not have a favorable prognosis, shown by the relative survival estimates of 5.6%, 5 years after diagnosis.[8]

Primary GBMs are differentiated from secondary GBM by many means including genotype, incidence, age of diagnosis, location, and presence of precursor lesion. Histologically, primary and secondary GBMs are very similar, except that primary lesions typically have more extensive necrosis.[6,9] Primary GBMs, also known as IDH-wild type, make up nearly 90% of all GBMs and present without a precursor lesion. Primary GBMs have a median age at diagnosis of 62 years old in the supratentorial location.[6,9] Secondary GBMs, also known as IDH mutant, present at a median age of 44 years old and with a Grade I or Grade II glioma precursor lesion. Secondary GBMs have a median overall survival of 24–31 months, in comparison to the poorer prognosis of 9.9–15 months for primary GBM.[6]

There is no current standard of care for GC. Surgery has limited therapeutic intervention due to the diffuse nature of the tumor.[4] Due to the lack of randomized clinical control trials, the effects of specific therapeutic interventions are unknown.[3] The current standard of care for GBM includes surgical resection, radiation, and chemotherapy.[10] There were statistically significant increased survival rates among patients that underwent surgical debulking, radiotherapy with concomitant temozolomide, followed by adjuvant temozolomide therapy, then compared with radiotherapy alone, 14.6 months and 12.1 months, respectively.[10] More aggressive surgical resections for GBM, when safely possible, are found to have better prognostic value for patients. Complete resection of GBM had significantly longer survival times, a median of 4.9 months, postoperatively compared to those with incomplete resections.[11] Multimodal therapy has been determined as the standard of care for GBM, but there is still a need for improved treatment outcomes, as GBM is still a devastating diagnosis with a poor prognosis.

CONCLUSION

An 81-year-old male with a primary GBM and unusual widespread diffuse infiltrating glioma extends throughout the cerebral hemispheres and brainstem. The diffusely infiltrating glioma in this patient is consistent with the previously categorized diagnosis of the rare GC type 2. Tumors of the central nervous system can present with variability of neurological deficits. In the current case, the clinical presentation was unusual with stroke-like symptoms which rapidly resolved. More studies are needed to determine the cause for the unusual diffuse growth pattern and further potential effects on the patient outcomes. High-grade gliomas, GBMs, are the most common malignant primary brain neoplasm and have a poor prognosis for patient survival. The current standard of care is non-existent for GC and has only progressed little since the establishment of the multimodal therapeutic approach for GBM.[10] While new treatments are being studied that increase quality of life and overall survival, there is a vast room for improvement in the treatment of GC and GBM for patients and their families.

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