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Case report

A rare case of gliomatosis cerebri lurking beneath the shadows of a stroke mimic ☆,☆☆,★

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ABSTRACT

Gliomatosis cerebri (GC) is a diffuse infiltrative neoplastic glial process with a devastating prognosis. Considering its rarity, unpredictable clinical manifestations, and lack of characteristic radiographic features, GC is a difficult diagnosis that is quite often delayed. In this report, we present a case of a 61-year-old man with a history of chronic alcohol abuse and atrial fibrillation who presented with right arm weakness initially presumed to be from an acute ischemic stroke. GC was not diagnosed until six months after initial symptoms and diagnosis was indicated when considering the neurocognitive findings in conjunction with suggestive radiographic findings. The presence of a rapid, expansile lesion in the cortex, corpus callosum, and infratentorial structures with mild parenchymal enlargement, as shown in our case, is more revealing of an invasive entity typical of GC rather than an ischemic process and other pathologies. This case demonstrates the fatal challenges of its prompt recognition and the therapeutic limitations for those patients presenting with advanced symptoms at the time of diagnosis. Recognizing GC in cases with such rapid multilobe clin-

Abbreviation: Gliomatosis Cerebri, (GC); Magnetic Resonance Imaging, (MRI); Fluid attenuated inversion recovery, (FLAIR); Computed tomography, (CT); Lateralized periodic discharges, (LPDs); Central nervous system, (CNS).

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ical features with similar diffusely invasive patterns of growth on imaging can avoid a delay in diagnosis and improve patient quality of life.

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Introduction

Gliomatosis cerebri (GC) is characterized as a rare, diffusely infiltrating, glial tumor with a relentless progression involving at least three cerebral lobes. Prognosis is poor, with a 30-month median survival time from diagnosis and a 50% mortality rate by one year [1–4]. GC remains a controversial neoplastic glial process lacking a consensual definition and diagnosis. Clinical presentation is nonspecific, location dependent, and typically an insidious reflection of its invasive nature. Common symptoms include focal neurological deficits, headache, symptoms of increased intracranial pressure, seizure, memory loss, and other neurocognitive impairments. Definitive diagnosis is made radiographically via magnetic resonance imaging (MRI) followed by tissue biopsy and histopathologic confirmation. Signaling patterns of the involved areas on brain MRI often show T1 weighted sequence hypo- or iso-intensity and T2/fluid attenuated inversion recovery (FLAIR) hyperintensity [1,5,6].

While imaging features are helpful in suspected GC cases, such enhancement patterns make a radiological diagnosis difficult due to the relatively low specificity [5,7]. These imaging findings can mimic other pathological processes, and patients are often misdiagnosed with other neurological diseases such as viral encephalitis, cerebrovascular pathology (e.g., ischemia), inflammatory diseases (e.g., vasculitis), and inflammatory demyelinating diseases [1,5,7]. There is no standard treatment for patients with GC and patients tend to present later in the disease course due to its rarity and difficult diagnosis. Despite aggressive treatment, patients have a poor outcome and the disease typically progresses rapidly. While the tumor comprises a diagnostic challenge, it can more confidently be indicated over other similarly presenting pathologies (eg, ischemia, demyelination) when considering the clinical context and neurocognitive findings in conjunction with suggestive radiographic findings.

Case presentation

We describe a case of a 61-year-old male with a medical history of atrial fibrillation and alcohol abuse who presented to the neurology clinic with right arm weakness for 2 weeks. Initial brain MRI indicated a 20 × 15 mm acute ischemic stroke in the left precentral gyrus extending to the left thalamus. The presumed etiology was cardio-embolic due to history of atrial fibrillation and the patient was started on aspirin and apixaban.

Over the course of the next few weeks, the patient presented to the emergency department on multiple occasions for worsening dysphagia and right-sided weakness, as well as

new-onset uncontrollable spastic hand movements. No evidence of fever or leukocytosis was noted during all hospital visits. Non-contrast computed tomography (CT) of the head demonstrated a small area of hypodensity in the left precentral gyrus and in the left basal ganglia. CT angiography of the head and neck revealed no stenosis, aneurysm, or vascular malformation. Repeat MRI of the brain demonstrated subacute increased size of previous ischemic stroke without acute findings (Fig. 1). His symptoms were presumed to be residual from initial stroke and he was discharged home with outpatient follow-up.

His symptoms progressively worsened the ensuing months, exhibited by a decline in his speech and ambulation. He also began to experience dysphagia and unintentional weight loss. His right-sided hemiplegia progressed to hemiparesis and he soon developed significant aphasia. Serial MRI of the brain demonstrated an acute/subacute extension of previously presumed stroke in the left precentral gyrus extending to the left thalamic regions associated with confluent areas of hyperintense signal on FLAIR and T2 imaging in these areas. MRI findings later showed what appeared to be chronic infarcts of left posterior frontal lobe, left centrum semiovale, and basal ganglia and T2/FLAIR hyperintensities attributed to white matter atrophy in the left brainstem. Imaging also showed a demyelinating appearance around the corpus callosum and adjacent subcortical and cortical white matter.

Six months after his initial presentation, the patient presented non-ambulatory and non-verbal with acute encephalopathy and multiple seizure episodes. EEG was performed which revealed lateralized periodic discharges with superimposed fast activity (LPDs+F) suggestive of a highly active area of epileptogenic potential in the left hemisphere and diffuse organized slowing. The patient was then transferred to a tertiary care center for EEG monitoring which continued to show LPDs+F. Final MRI brain exhibited T2/FLAIR hyperintensity throughout large portions of the left frontal, parietal, and temporal lobes, extending into the thalamus and mid-brain along the corticospinal tract with associated mass effect (Fig. 2). Abnormal FLAIR and T2 signals were also seen within the pons, superior cerebellar hemispheres, and middle cerebellar peduncles, as well as extending across the body of the corpus callosum. New areas of T2 hyperintensity were noted within the lateral right precentral gyrus and right corona radiata. Post-contrast T1-weighted imaging demonstrated no abnormal enhancement (Fig. 3). These findings were most consistent with a diffusely infiltrating glioma exhibiting GC pattern of growth. The patient did not undergo a brain biopsy due to worsening clinical condition and poor prognosis. The patient was later discharged to hospice care and expired shortly thereafter. His death was seven months from the time of initial presentation presumably due to disease progression.

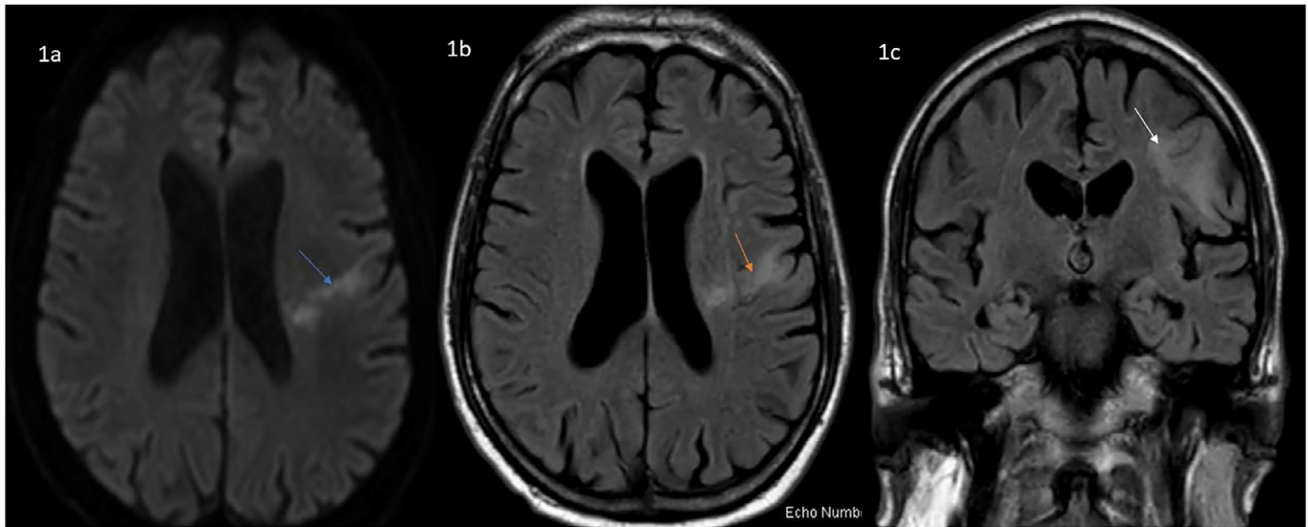


Fig. 1 – Diffusion weighted imaging axial (DWI) (1a; blue arrow), FLAIR axial (1b; orange arrow) and FLAIR coronal (1c; white arrow) revealed a 20 × 15 mm focus of restricted diffusion and hyperintense FLAIR signal of what appeared to be an acute to subacute ischemic infarction in the left precentral gyrus extending to the left thalamus found on early presentation

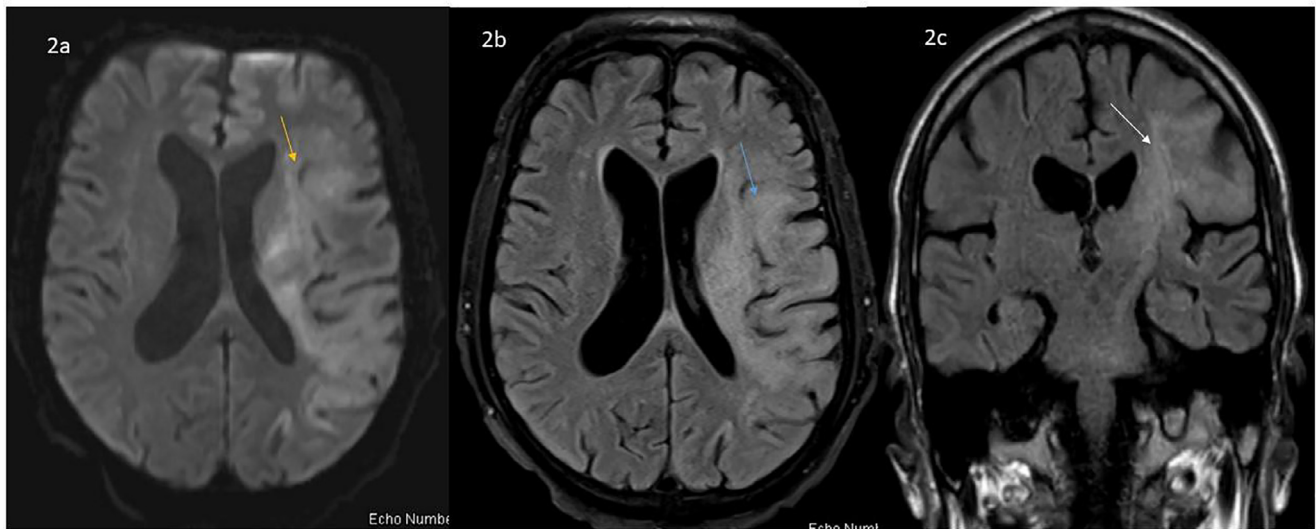


Fig. 2 – Diffusion weighted imaging (DWI) axial (2A; yellow arrow), FLAIR axial (2B; blue arrow) and FLAIR coronal (2C; white arrow) six months after initial presentation, DWI (2A) and FLAIR (2B) demonstrated interval expansion of restricted diffusion and FLAIR hyperintensity throughout large portions of the left frontal, parietal, and temporal lobes with associated mass effect. Findings were most consistent with infiltrating glioma (gliomatosis cerebri)

Discussion

Previously classified as a distinct pathological entity, according to the 2007 World Health Organization (WHO) classification of central nervous system (CNS) tumors, GC refers to a unique pathological process of a diffuse glioma that infiltrates a large portion of the neuroaxis [8]. This rare entity represents a lethal disease manifestation with an exclusive phenotype and is considered a continuum from other gliomas [1]. The

overall incidence rate is 0.15 cases per million individuals, and this tumor contributes to only 1/500 of all malignant CNS tumors [4]. GC affects all age groups with a median age and peak incidence between 40 and 50 years with a slight male predominance [2,3,9]. Prognosis is poor, with one-year and five-year overall survival rates lower than 50% and 20%, respectively, and a median overall survival ranging from 7 – 18.5 months [4,10]. Further, worse outcomes are noted in tumors involving the deep cerebral structures and infratentorial structures compared to tumors confined to the cerebral hemispheres [4].

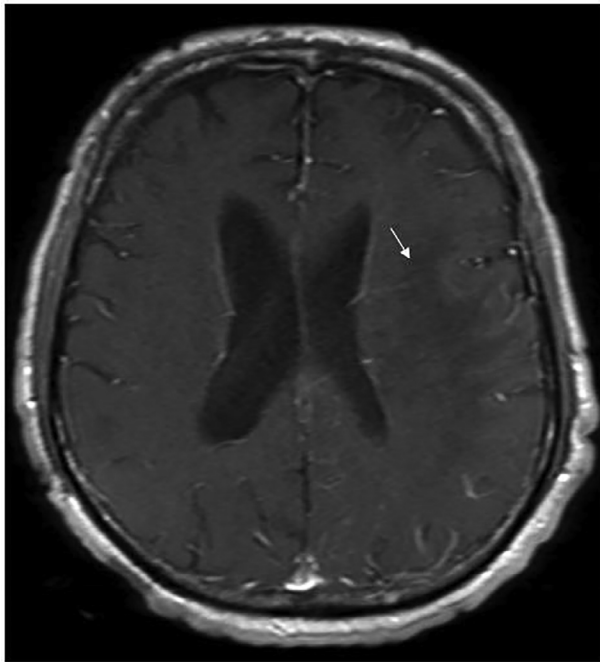


Fig. 3 – T1 weighted post-contrast imaging demonstrates no enhancement of the involved areas of the brain. Findings were most consistent with infiltrating glioma (gliomatosis cerebri)

The clinical presentation is variable due to the multiple structures involved by virtue of its widespread infiltration. There are no classic manifestations owing to the extensive invasive nature of this tumor. Presenting symptoms are typically location dependent and insidious, which often delay diagnosis. Common complaints include seizures associated with frontal and temporal lobe involvement; headache or manifestations of increased intracranial pressure; focal motor deficits associated with motor cortex or corticospinal tract involvement; gait abnormalities associated with cerebellar or spinocerebellar involvement; cranial nerve palsies associated with brainstem or corticobulbar tract involvement; and cognitive decline or memory deficits associated with infiltration of the parietal and occipital lobes and corpus callosum [1,5,9]. The clinical findings in this case included right-sided weakness corresponding with involvement of the left precentral gyrus and corticospinal tract; dysphagia and aphasia most likely related to precentral gyrus, corticobulbar tract, and/or brainstem involvement; gait abnormalities corresponding with cerebellar and/or spinocerebellar tract involvement; and seizures associated with frontal and temporal lobe involvement.

MRI is considered the superior imaging modality. Because the clinical manifestations of GC can be nonspecific, MRI has been used as a powerful paraclinical tool. GC invades at least 3 contiguous cerebral lobes and predominantly involves the cerebral white matter first. The neoplastic process typically spreads to the corpus callosum, followed by bilateral hemispheric invasion [11]. Expansion may eventually affect the deep gray matter (basal ganglia, thalamus), cerebellum, brain-

stem, and possibly the spinal cord. The involved areas on MRI typically show T1-weighted iso- to hypo-intensity and T2-weighted or FLAIR hyperintensity [1,5]. Imaging shows diffuse infiltration and may include poor gray-white matter distinction; mild expansion or distortion of the involved areas; and typically lacks contrast enhancement. Macroscopically, the glial tumor cells appear as a homogenous mass with expansion of the parenchyma without disrupting the normal brain architecture [11]. A systematic review by Georgakis et al. found diffuse hyperintensities in T2/FLAIR sequences in 100% of the 1237 GC cases and areas of post-contrast enhancement in T1 sequences in 36% of patients on neuroimaging [5].

The non-specific features of a patient's clinical presentation and neuroimaging findings contribute to a broad differential diagnosis when considering GC as the responsible entity. This is a major challenge to a timely diagnosis. The neurocognitive deficits in addition to diffuse T2 hyperintensities noted in GC cases can also be found in many other pathologies, including demyelinating diseases (eg, multiple sclerosis, progressive multifocal leukoencephalopathy, acute disseminated encephalomyelitis), vasculitis, encephalitis, and ischemia [1,11,12]. However, an extensive lesion infiltrating the cerebral white matter, corpus callosum, cerebellum, and brainstem, as seen in this case, narrows the differential diagnosis to a neoplasm (i.e., infiltrating glioma or lymphoma) and a demyelinating process. A few pertinent negative clinical and laboratory findings of this case made encephalitis and PML less likely, including lack of a fever or leukocytosis and lack of HIV or immunocompromised state. Initial presentation of our case appeared to resemble an ischemic stroke and later a demyelinating disease. This case demonstrated macroscopic features on neuroimaging supporting a neoplastic process. The presence of an expansile lesion in the cortex, corpus callosum, and infratentorial structures (e.g., brainstem, cerebellum, spinal cord) and parenchymal enlargement as shown in our case is more revealing of a tumor rather than an ischemic process, vasculitis, and demyelination [12]. Further, a lack of contrast enhancement distinguishes the tumor from a lymphoma. While white matter atrophy was noted on MRI, significant confluent cerebral and deep gray matter involvement suggests neoplasm instead of demyelination [13]. Lastly, EEG findings for GC patients have shown inconsistencies and non-specific abnormalities [5]. Our case exhibited LPDs+F diffusely over the left hemisphere on continuous EEG monitoring which correlated with MRI findings of a diffusely infiltrative lesion involving much of the left hemisphere. While LPDs are recognized as uncommon with an uncertain significance and found in many disease states (e.g., cerebrovascular disease, brain lesions, metabolic disturbance, seizures), these findings in conjunction with the clinical features suggest that the etiology of the patient's seizures was most likely related to tumor infiltration of the overlying cortex [14].

Diagnosing GC is controversial as there are no consensual clinical, radiographic, and histological findings that are diagnostic. Recent studies noted an emphasis on the importance of MRI and MR spectroscopy in the diagnostic evaluation and, furthermore, a tendency of radiological methods to substitute the gold-standard histological diagnosis [4,5]. There remains a continuous trend of increased radiologically diagnosed GC cases. A large case series by Georgakis et al. found that clin-

ically and/or radiologically diagnosed tumors were reported in 36% of the GC patients [4]. Similarly, this case was radiologically diagnosed, as histological confirmation was not performed due to the patient's rapidly deteriorating condition. In addition to the clinical presentation, radiographic evidence was significant for an invasive entity typical of GC. Though there remains an absence of distinct molecular or histologic features compared to other diffuse glial tumors, GC has a unique invasive pattern with such rapid diffuse spread unparallel to similar grade gliomas. GC patients include a shorter survival compared to other patients with gliomas of corresponding histologic grade [3].

Treatment of GC is challenged by the fact that there is no standard of care. Patients typically present later in the disease course, as its insidious spread often goes misdiagnosed. When patients present with advanced symptoms and a significant tumor burden at the time of diagnosis, treatment options are limited. The role of surgical therapy primarily encompasses diagnostic purposes (i.e., tissue biopsy) and decompression for symptomatic improvement [1,6]. Adjuvant chemotherapy and radiotherapy demonstrate minimal efficacy and the impact on survival remains unclear [7].

Conclusion

In conclusion, our study demonstrates the fatal challenges of prompt recognition and therapeutic limitations for those patients presenting with advanced symptoms of GC at the time of diagnosis. As consistent characteristic disease features have not been established, the tumor remains an inherently difficult diagnosis. Nevertheless, it is important to consider the clinical context and neurocognitive manifestations in conjunction with the radiographic findings. Multiple features observed in our case suggested GC over more common pathologies, including an expansile lesion infiltrating the multilobe cerebral white matter, deep gray matter, and infratentorial structures, lack of contrast enhancement, and parenchymal enlargement. This case emphasizes the importance of serial MRI assessments in the diagnostic evaluation of patients when suspicious of diffuse glioma. Although prognosis is poor, a timely diagnosis may contribute to some short-term survival benefit.

Author Contributions

Conceptualization: Apoorv Prasad *Writing Original draft preparation:* Apoorv Prasad, Gage Hurlburt, Emily Van Antwerp, Samiksha Srivastava, Shitiz Sriwastava

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