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Understanding the Brain-Heart Connection Through a Case of Angry Glioma Syndrome

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We discuss a patient with a tumor on the anterior corpus callosum who underwent open biopsy eventually succumbing to cerebrogenic fatal arrhythmia following wounded glioma syndrome. A healthy 37-year-old female patient was admitted to our department due to a history of headache for 13 months. MRI revealed a suspicious glioma infiltrating the anterior corpus callosum. Neurologic examination only showed low cognitive assessment score (Montreal Cognitive Assessment score 20/30). ECG was normal sinus rhythm. Steroids and levetiracetam were administered prior to operation. Patient underwent right frontal craniotomy and biopsy of tumor with unremarkable events. During the first hospital day, patient had episodes of bradycardia followed by decrease in sensorium. Brain CT scan showed progression of edema without hemorrhage within the tumor bed. This was followed minutes later by two episodes of generalized tonic-clonic seizures and pulseless ventricular tachycardia. Cardiac resuscitation was done for 24 minutes but patient eventually expired. Location of the lesion and the epileptogenicity of the peritumoral cortex greatly contributed to the patient's demise. Involvement of the fronto-mesial structures, particularly the insula and the cingulate cortex, and their connection to the central autonomic network, increased susceptibility to arrhythmias. Decreased seizure threshold worsened post-operative edema, further aggravating the dysregulation of the brain-heart-connection.

Keywords Glioblastoma; Brain neoplasm; Biopsy.

INTRODUCTION

Wounded glioma syndrome is a rare complication observed after incomplete tumor resection, resulting in edema or hemorrhage within the tumoral bed arising from the disruption of the tumor's richly vascularized tissue [1]. The resulting peritumoral border, known to be a highly epileptogenic area, also predisposes patients into having new-onset seizures after tumor resection [2]. Depending on its location within the cerebral cortex, these complications may affect the brain's ability to modulate cardiac activity through its influence to the autonomic nervous system and neurocardiac reflexes that influence autonomic outflow [3]. In this study, we discuss a patient with a tumor on the anterior corpus callosum who underwent open biopsy, eventually succumbing to cerebrogenic fatal arrhythmia.

CASE REPORT

A 37-year-old female patient was admitted to our hospital for a history of headache and memory lapses for 13 months. MRI revealed a suspicious butterfly glioma infiltrating both bilateral frontal lobes, anterior cingulate gyri, rostrum, genu and anterior body of the bilateral corpus callosum (Fig. 1).

Neurologic examination revealed a low cognitive assessment score (Montreal Cognitive Assessment [Filipino version]) of 20/30. She has no other known medical comorbidities or history of seizures. The patient did not complain of any cardiac symptoms previously and cardiorespiratory work-up was unremarkable. Electrocardiogram (ECG) pattern on admission was normal sinus rhythm. Vital signs prior to the operation were all within normal ranges, and the patient was subsequently cleared as low risk for perioperative complications. The following medications were started for prophylaxis: dexamethasone 5 mg intravenously every 6 hours, mannitol 150 mL (0.5 g/kg) intravenously every 4 hours, and levetiracetam 500 mg intravenously every 12 hours. The patient underwent right frontal

craniotomy and biopsy of tumor with frozen section (Fig. 2) with no intraoperative complications.

On the first hospital day, the patient had episodes of bradycardia as low as 30 beats per minute followed by decrease in sensorium. A repeat brain CT scan (Fig. 3) was done which showed progression of edema at the level of the frontal horn of both lateral ventricles, with no signs of bleeding or hemorrhage.

A few minutes later, the patient was referred for two episodes of generalized tonic-clonic seizures followed by pulseless ventricular tachycardia and asystole. Intubation was done and the patient was resuscitated after 24 minutes of arrest time. Levetiracetam was given with a loading dose of 3.8 g intravenously

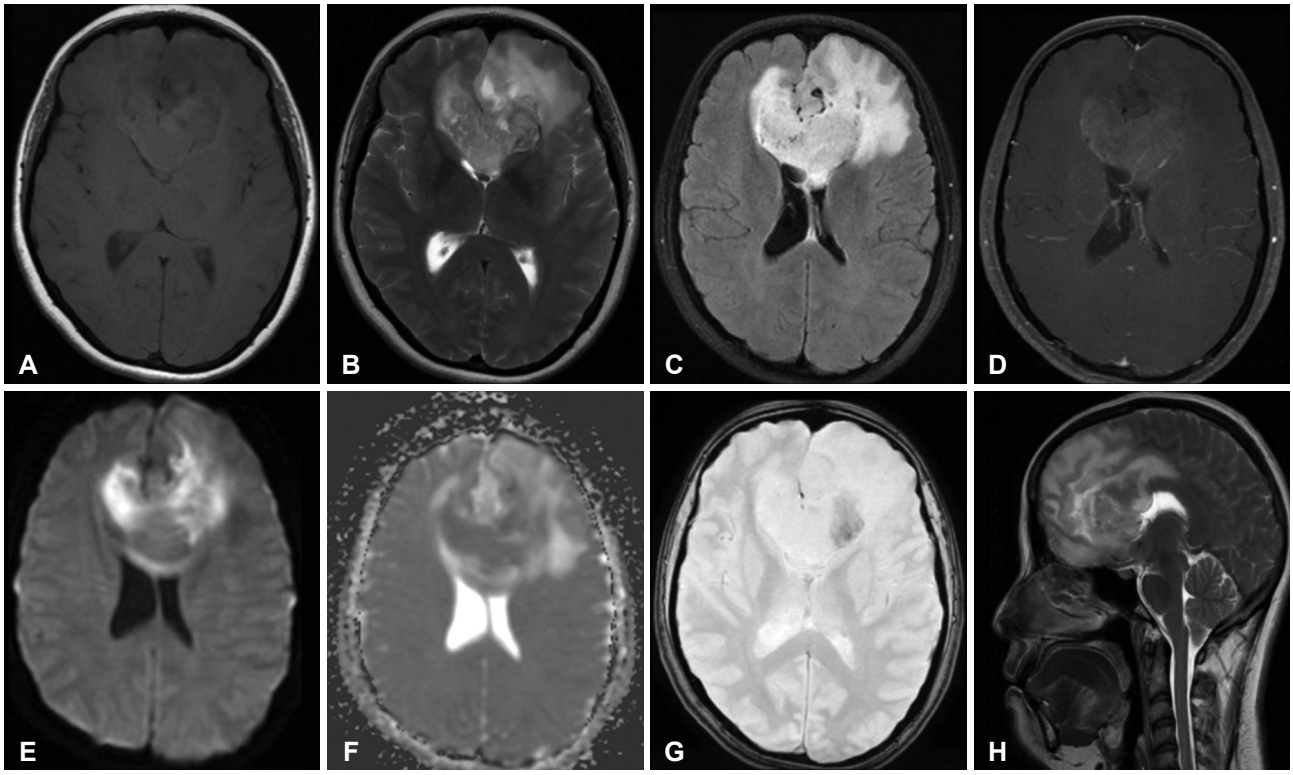

Fig. 1. Preoperative MRI. A and B: T1-weighted (A) and T2-weighted (B) images showed a mixed intensity predominantly hyperintense representing areas of microcystic changes involving the bilateral frontal lobes, anterior cingulate gyri, rostrum, genu and anterior body of the bilateral corpus callosum. C: Fluid attenuated inversion recovery image showing the extent of the lesion. D: Noted faint enhancement on gadolinium contrast. E and F: Diffusion-weighted imaging (E) and apparent diffusion coefficient (F) showing restricted diffusion in some areas within the lesion. G: Gradient echo susceptibility shown representing areas of necrosis. H: Sagittal view of the lesion.

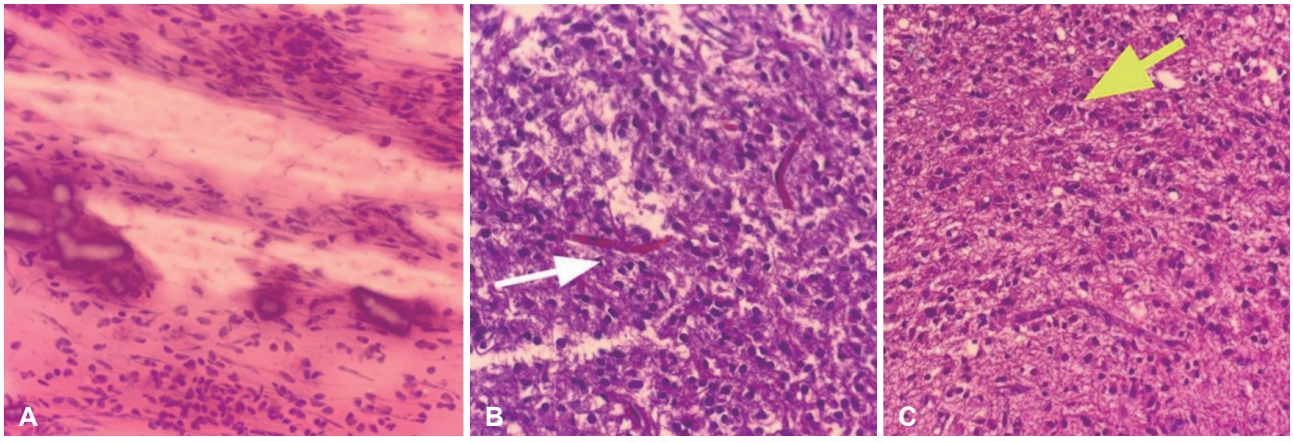

Fig. 2. Histopathology of the tumors. A: On frozen section, a crush preparation was done showing cells with epithelioid and spindle cell features. Nuclei appear low grade and do not exhibit pleomorphism (H&E, ×100). B: High power view shows a very cellular specimen, with evidence of perivascular satellitosis (white arrow) (H&E, ×200). C: Evidence of perineuronal satellitosis was also noted (yellow arrow) (H&E, ×200).

and dexamethasone was increased to 10 mg intravenously every 4 hours. The patient was then subsequently referred to cardio service who diagnosed the patient as a case of cerebrogenic arrhythmia. EEG monitoring and further cardiac work-up were offered but due to poor prognosis and financial constraints, family opted for maximum medical management only. The patient eventually expired on the 6th hospital day.

Final immunohistochemical stains (Fig. 4) revealed positivity for OLIG2 and Ki-67. Further staining was not done due to the patient's financial constraints. The case was eventually signed out as cerebrogenic fatal arrhythmia secondary to status epilepticus secondary to angry glioma syndrome from diffuse butterfly glioma, not otherwise specified.

DISCUSSION

Angry glioma syndrome

Angry glioma syndrome or wounded glioma syndrome is a rare complication usually observed after incomplete tumor resection which results in the disruption of the tumor's richly vascularized tissue or through local hemodynamic changes causing decreased regional blood flow and loss of autoregulation resulting in either bleeding or peri-tumoral edema of the tumoral bed [1]. A few case reports have been written on the subject for the past two decades. Koebbe et al. [4] described two cases of peri-tumoral cavity bleed occurring on distant tumor nodules from the partially resected site. A rare case report on wounded glioma syndrome following stereotactic biopsy was also documented [5]. Krajewski et al. [1] described two unusual cases of malignant swelling and rapid fatal outcome on two young individuals following both open and stereotactic biopsies.

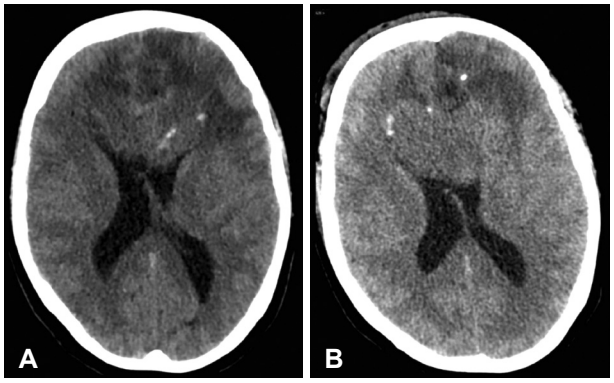

Fig. 3. Preoperative CT scan (A) compared to postoperative CT scan (B) showed progression of edema involving the bilateral frontal lobes, now effacing most of the frontal horns of the lateral ventricles but with no signs of hemorrhage within the tumor.

Peritumoral neocortex

Understanding the pathophysiology of wounded glioma syndrome requires knowledge of the peritumoral neocortex. The "peri-tumoral border," or the area where the tumor and the normal brain meet, is a highly epileptogenic area since network organization happens particularly within its supragranular cortical layers, thus, making it possible for patients with no previous history of epilepsy secondary to a brain tumor, to develop new-onset seizures post-resection [2]. Microscopically, there is a breakdown in glutamate homeostasis particularly the upregulation of cystine/glutamate antiporter system which increases glutamate production [6]. This is further exacerbated by the downregulation of the astrocytic glutamate transporter which prevents the clearance of glutamate from the synaptic cleft ultimately leading to an increase in neuronal hyperexcitability [7].

The brain-heart connection

The brain and the heart maintain a two-way relationship: First is through the influence of the autonomic system as the final effector that modulates cardiac activity; Second is through neurocardiac reflexes that influence autonomic outflow [3].

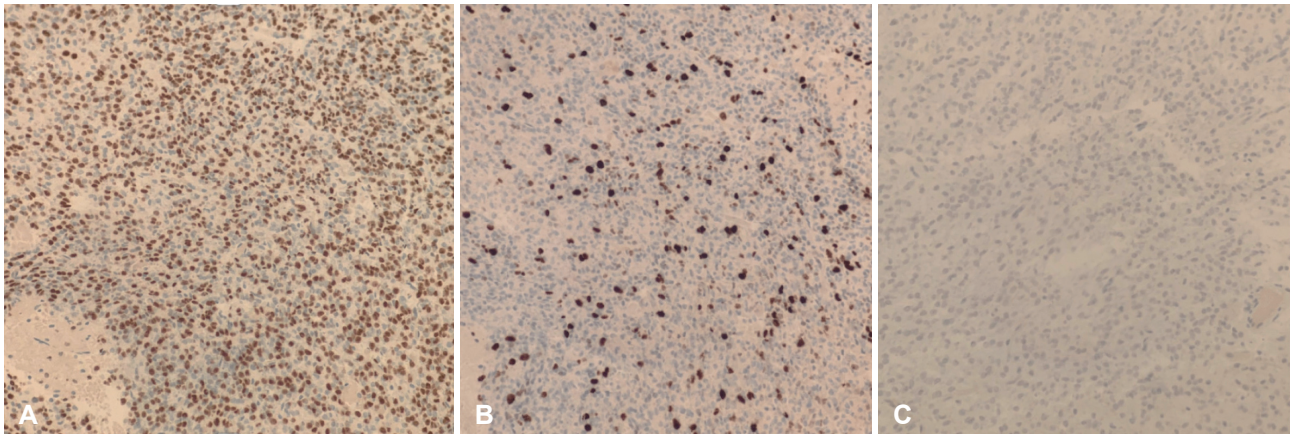

Fig. 4. Immunohistochemical stains. A: Sample is positive for OLIG2 (×100). B: Positive for Ki-67 (×100). C: Negative for IDH1 R132H, p53, and ATRX (×100).

Cardiac arrhythmia can happen at multiple levels within the brain. Of interest in our case is the involvement of the salience network. This network is an intrinsic interconnection between the frontal lobe, anterior insula, and the dorsal anterior cingulate cortex, acting as the brain's "moderator" for sensorimotor processing, general cognition, pain, reward, and physical action [8]. In particular, the posterior insula processes somatosensory, visual, and motor stimuli as well as the body's own physiological condition [9]. The medial hemispheric surface of the frontal lobe, where the anterior cingulate cortex lies, is also strongly implicated in efferent cardiovascular drive through dorsal anterior cingulate activation, and ventral anterior cingulate deactivation causing diminished parasympathetic function [3].

Cortical stimulation studies in humans have shown depressor responses upon stimulation of the left insular cortex, whereas the opposite is applied to the right insular cortex [10]. The central autonomic network governs heart rate and contractility at rest and during physical, emotional, and psychological challenge [11]. This extrinsic cardiac network, distributed throughout the neuraxis, has preganglionic parasympathetic neurons located in the nucleus ambiguus and to the dorsal motor nucleus of the vagus, that innervate the sinoatrial node, both atria, atrioventricular node, and the ventricular conducting system [12]. Noradrenergic post-ganglionic fibers, in turn, richly innervate the left and right atria and, in part, the ventricles [13].

Thus, it is hypothesized that seizures originating in the fronto-mesial structures may disrupt the complex neural system involving the fronto-temporal-insular regions, and these regions have been implicated in the autonomic regulation of the cardiovascular responses [3].

Conclusion

The location of the patient's lesion, in addition to the innate epileptogenic nature of the peritumoral cortex, has greatly contributed to the postoperative course and eventual demise of the patient. Involvement of the fronto-mesial structures particularly the insula and the cingulate cortex and their connection to the central autonomic network made the patient with no known cardiac comorbidities, susceptible to a cardiac event, particularly that of bradycardia and asystole. On the other hand, changes in the molecular structure of the peritumoral cortex particularly the upregulation of glutamate and the downregulation of its clearance may have caused the seizure episode which could have further aggravated the postoperative edema, further causing dysregulation of the brain-heart connection.

Ethics Statement

The Institutional Review Board (IRB) exempted informed consent due to its retrospective descriptive nature (case report) and minimal risk for harm to the patient.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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