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CASE REPORT **OPEN ACCESS**

NEW-ONSET INTRACRANIAL HEMORRHAGE IN A PATIENT WITH GLIOBLASTOMA MULTIFORME: A CASE REPORT

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ABSTRACT

Background: Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults. GBM is a high-grade glioma of the central nervous system associated with high morbidity and/or mortality, often accompanied by Intracranial Hemorrhage (ICH).
Case: This study reports a 62-year-old male patient presenting with sudden-onset weakness in the left extremities, which worsened over the past week, without any history of trauma. A non-contrast computed tomography (CT) scan of the head revealed the presence of ICH. Laboratory findings showed leukocytosis and mild hyponatremia. The patient had previously been diagnosed with glioblastoma in the right parietal region, confirmed through magnetic resonance imaging (MRI), which revealed multiple lesions with solid-cystic components. The patient had undergone tumor removal surgery via craniotomy for further histopathological examination. A repeat craniotomy was performed to evacuate the ICH. Following the evacuation of the hemorrhage, clinical improvement was observed.
Discussion: GBM classically presents with symptoms of increased intracranial pressure and gradually progressive neurological deficits. GBM also enhances vascular endothelial growth factor (VEGF) activity, contributing to the increased incidence of ICH. Acute presentation with ICH and rapid clinical deterioration is rare. The current treatment options for GBM are multimodal, including surgical resection, radiation therapy, and chemotherapy.
Conclusion: GBM presenting with ICH is uncommon but life-threatening. This case underscores the need for high clinical suspicion and immediate neuroimaging in patients with known or suspected GBM presenting with acute neurological decline. Timely surgical intervention can improve outcomes.

Keywords: glioblastoma multiforme, hemiparesis, hemorrhagic stroke

Introduction

Glioblastoma multiforme (GBM) is the most common type of malignant primary brain tumor, accounting for over half of all primary malignant tumors in the Central Nervous System (CNS).[1] GBM is a WHO grade IV (most malignant) brain tumor, which represents one of the most lethal human cancers. The incidence is higher in men than in women. The median overall survival (OS) of GBM patients is low, at only 15 months. The exact cause of GBM is unknown. However, two main genetic pathways are involved in its development: primary and secondary GBM. Several factors are believed to significantly contribute to tumor growth, including the activation of oncogenes, the loss of tumor suppressor genes, and the involvement of growth factors. The clinical symptoms of GBM significantly depend on the tumor's location, size, and growth rate. Common symptoms include headaches, weakness in the arms and legs, personality changes, seizures, vision disturbances, and cognitive decline.[2]

GBM has been classified into isocitrate dehydrogenase (IDH) wild-type and mutant variants. IDH variants bear the cytosine-phosphate-guanine (CpG) island methylation phenotype (G-CIMP).[3] IDH wild type, arising de novo, constitute almost 90% of all GBM. They

are usually observed among cohorts older than age 55 years. Histologically, they comprise the giant, gliosarcoma, and epithelioid cell subtypes. They are associated with mutations in the epidermal growth factor receptor (EGFR), the telomerase reverse transcriptase gene (TERT), or the O-methylguanine DNA methyltransferase (MGMT) gene.[4] IDH-mutants arise from precursor diffuse or anaplastic astrocytoma. They are associated with ATRX and TP53 mutations and typically affect younger patients. They comparatively have longer median survival rates.[4,5]

Intracerebral hemorrhage (ICH) is the second most common type of stroke and a critical disease usually leading to severe disability or death. ICH is usually caused by rupture of small penetrating arteries secondary to hypertensive changes or other vascular abnormalities.[6-9] The primary pathoetiologies of spontaneous ICH are chronic hypertension and cerebral amyloid angiopathy (CAA). Secondary pathoetiologies are bleeding from imageable vasculopathies and tumors, and hemorrhagic conversion of ischemic stroke or venous thrombosis. Coagulopathy, platelet dysfunction, and illicit drug use can contribute to ICH or its severity.[10-12]

GBM and ICH are very different conditions. GBM is a significant risk factor for ICH in patients. This study presents a case of a 62-year-old male with ICH and GBM.

Case Report

A 62-year-old male with no significant past medical history was admitted to the Emergency Room of Dr. R. Soetrasno Rembang General Hospital with a sudden onset of weakness affecting his left upper and lower extremities. The weakness had worsened progressively over the past week and was not associated with any history of trauma. The symptoms began seven days before admission and were accompanied by slurred speech, headache, nausea, and vomiting, along with progressive deterioration in motor function on the left side of the body. The patient was hospitalized in the High Care Unit (HCU) for three days for close observation and supportive management.

Two months earlier, the patient had experienced a generalized seizure involving the whole body and was hospitalized for three days at the same hospital. Following this episode, he attended a follow-up consultation at the neurosurgery department of Dr. Moewardi General Hospital, where a contrast-enhanced brain MRI was performed (Figure 1). A histopathological examination of brain tissue from the right parietal lobe confirmed the diagnosis of glioblastoma (WHO Grade IV) (Figure 2). Due to persistent left-sided weakness with no clinical improvement, the patient's family brought him to the Emergency Department of Dr. Moewardi General Hospital for further evaluation and management.

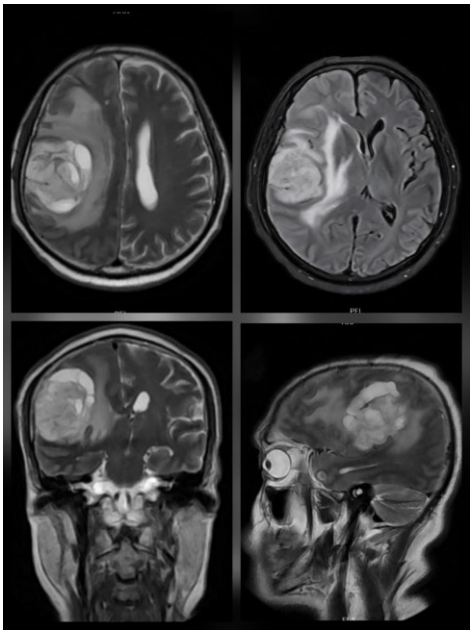

Figure 1. RI brain contrast shows multiple intra-axial supratentorial lesions with mixed intensity, consisting of solid, necrotic, and hemorrhagic components of varying ages, present in the right parietal and right temporal lobes. These lesions exert pressure and narrow the right lateral ventricle's anterior, temporal, and posterior horns, causing subfalcine herniation of 0.44 cm to the left and compressing the mesencephalon, suggesting a metastatic process.

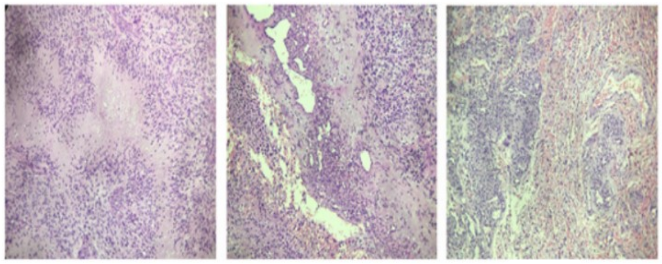

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Figure 2. a) The specimen shows fragments of brain tissue with a tumor infiltrating the surrounding tissue, accompanied by areas of pseudopalisading necrosis. b) The tumor cells are polymorphic, medium to large, mostly with scant to moderate eosinophilic and partially fibrillary cytoplasm. The nuclei are round to oval in shape with irregular membranes and coarse chromatin, some of which is hyperchromatic. c) Mitoses are observed. Numerous blood vessels exhibited endothelial hyperplasia in other areas, some forming glomeruloid patterns

Physical examination demonstrated compos mentis sensorium with a Glasgow Coma Scale Score of 15 (E4M6V5), blood pressure of 127/74 mmHg, heart rate 90 bpm, respiratory rate 20 bpm, SpO2 99% on room air, and a temperature of 36°C, weakness on the left extremities with motoric strength 5555/4444. Physical examination revealed unremarkable findings in the lungs, heart, abdomen, and extremities, with no signs of infection.

A decompressive craniectomy was done for the lesion. A repeat craniotomy was performed to evacuate the ICH. Following the evacuation of the hemorrhage, clinical improvement was observed. Treatment post craniotomy was started on empirical intravenous antibiotic therapy, specifically intravenous ampicillin at 1 grams/8 hours, dantrolene at 5 mg/12 hours, mannitol at 100 cc/ 6 hours, and phenytoin loading dose 15 mg/kg, maintenance 500 mg/8 hours. Vital signs were continuously monitored. By the tenth day of hospitalization, clinical improvement was observed.

Discussion

Epidemiological studies show an increased incidence of ICH in brain tumor patients. GBM classically presents with symptoms of increased intracranial pressure and gradually progressive neurological deficits. GBM also enhances vascular endothelial growth factor (VEGF) activity, contributing to the increased incidence of ICH. Acute presentation with ICH and rapid clinical deterioration is rare.[14-16]

Ruptured blood vessels in a hemorrhagic stroke result in a decrease in cerebral blood flow, a mechanism for reducing bleeding, and if the hypoperfusion persists beyond several minutes, brain ischemia arises and brain cell hypoxia ensues. Hypoxic conditions may induce brain mesenchymal cells to change into glioma cells.[9] Ngb overexpression promoted the proliferation of neural progenitor cells (NPC), enhanced neuronal differentiation of cultured NPC under differentiation conditions, and promoted neurogenesis in the mouse brain after stroke.[17-20] During hypoxia, the brain expresses neuroglobin (Ngb) in neuronal and neuroglial cells to enhance the survival of brain cells. Ngb, a heme-containing protein, is involved in metabolizing reactive nitrogen and oxygen species, as well as in intracellular signaling pathways.[21]

In cultured neural (HN33) cells, overexpression of the hypoxia-inducible factor (HIF-1α) subunit through a lentiviral vector was found to double the expression of Ngb, indicating a strong association between HIF-1α levels and Ngb production. Ngb expression is also elevated in human glioblastoma cells under hypoxic conditions in vitro. Furthermore, increased Ngb enhances tumor survival by promoting proliferation and inhibiting apoptosis through the phosphatidylinositol 3-kinase (PI3K)/AKT pathway. This pathway regulates key factors in glioma cell proliferation, apoptosis resistance, and cell cycle progression, including mTOR, Bax, cyclin D1, Bcl-2, and Bcl-2-like 1. Specifically, mTOR supports cell survival and proliferation, while alterations in Bcl-2/Bax expression influence glioma cell apoptosis [22-24]

In cultured mouse astrocytes, Ngb counteracts oxidative stress by preventing Bax (a pro-apoptotic protein) activation and maintaining Bcl-2 (an anti-apoptotic protein) expression, thereby inhibiting caspase-3 activation. Astrocytes possess antioxidative mechanisms that help them survive ischemic conditions. Ischemic environments can induce astrocyte ischemic tolerance, reducing damage from subsequent mild ischemic events. Areas of focal brain hypoxia correlate with infarct regions, possibly due to impaired elimination of reactive oxygen species resulting from a deficiency in vimentin and glial fibrillary acidic protein (GFAP). The upregulation of GFAP is a marker of astrocyte reactivity, which is commonly observed in various neuropathological conditions, including stroke, neurotrauma, brain tumors, perinatal asphyxia, epilepsy, Parkinson's disease, Alzheimer's disease, and multiple sclerosis. In response to brain injury, glial cells begin expressing glial cell-derived neurotrophic factor (GDNF). Additionally, neuroinflammation can trigger the expression of GDNF in activated astrocytes, microglia, infiltrating macrophages, nestin-positive reactive astrocytes, and neuron/glia (NG2)-positive microglia-like cells. The role of Ngb in astrocyte proliferation remains unclear. However, following brain injury, reactive astrogliosis results in changes in molecular expression, astrocyte hypertrophy, and proliferation. As a result, tissue damage and inflammation contribute to the formation of glial scars, consisting of proliferating astrocytes, fibromeningeal cells, other glial cells, and collagen deposition in the extracellular matrix.[25]

Conclusion

GBM presenting with ICH is uncommon but life-threatening. This case underscores the need for high clinical suspicion and immediate neuroimaging in patients with known or suspected GBM presenting with acute neurological decline. Timely surgical intervention can improve outcomes. This report is limited by its single-case design and lack of long-term follow-up. The causality between GBM and ICH remains speculative, and larger studies are needed to better define risk factors and management strategies.

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