Glioblastoma following Hemorrhagic Stroke: A Case Report

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Abstract

Objective: To report a glioblastoma (GBM) case preceded by a hemorrhagic stroke.

Methods: This case reported a 53-year-old male presenting at at Murni Teguh Memorial Hospital, Medan, Indonesia, with a chief complaint of an altered mental state. The condition had been worsened for two weeks. On anamnesis, he was identified to have experienced intracerebral hemorrhage in January 2020. A follow-up head computed tomography scan was conducted in September 2020, showing a normal condition of the brain. Other oncogenic risk factors were not found. Due to convulsion in October 2020, the patient underwent a magnetic resonance imaging examination showing a cystic right temporoparietooccipital lesion and cerebral edema. Craniotomy tumor removal surgery was performed while the tumor was further examined for histopathological findings. The tumor was diagnosed as glioblastoma with microvascular proliferation and palisading necrosis.

Results: There was some associations between hemorrhagic stroke and glioblastoma development.

Conclusion: GBM preceded by hemorrhagic stroke is a rare case that can be diagnosed thoroughly by complete clinical and adjunct examinations.

Keywords: Brain tumor, glioblastoma, hemorrhagic stroke

Introduction

Stroke is a type of neurovascular disease that still remains as one of the major causes of disability, morbidity, and mortality in Indonesia.[1] Indonesian Basic Health Research (Riset Kesehatan Dasar) in 2018 reported that the prevalence of stroke increased as compared to 2013.[2]

Stroke is classified into ischemic and hemorrhagic one while the manifestation itself depends on the brain area involved. Ischemic stroke occurs when brain blood vessels were, either partially or totally, occluded by thrombus or embolus. On the other hand, hemorrhagic stroke occurs when the blood vessels in brain parenchyma rupture and the blood disseminates into subarachnoid space.[3] Furthermore, ruptured blood vessels induce hypoxic condition in the distal area of the ruptured vessels due to diminished blood vessels capability in delivering oxygenated blood. Hence, this hypoxic area lately may cause other brain cellular changes since neurons are highly oxygen-dependent cells in nature.[1]

Glioblastoma (GBM) is one of the most common primary malignant brain tumors. Due to its distinct biology and recurrence rate, the disease prognosis is poor despite optimal treatment such as surgical resection and aggressive adjuvant treatment were conducted.[4] GBM showed angiogenesis induced by vascular endothelial growth factor hypersecretion implying its invasiveness character. Correspond to its invasiveness nature, this tumor is challenging to be resected totally.[5] The advances of GBM

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biology and pathophysiology are critical to allow various novel therapeutic modalities including targeted therapy, gene therapy, and immunotherapy.[4]

GBM and hemorrhagic stroke are two different diseases. The GBM risk may increase in hemorrhagic stroke patients.[6] This study reported a case of 53-year-old male diagnosed with GBM with a hemorrhagic stroke history.

Case

An otherwise healthy 53-year-old male revealed that in 2 January 2020 he had brain surgery. Before that time, he presented spontaneous loss of consciousness and, subsequently, was diagnosed with intracerebral hemorrhage based on Head CT scan examination (Fig. 1).

Decompressive craniectomy was done for the lesion and skull reimplantation was performed 3 months afterward. He received a standardized herbal medicine namely Neuroaid®. After skull reimplantation, he fully recovered and completed the treatment. In September 2020, a follow up Head CT scan was performed and the conclusion was normal (Fig. 2).

In October 2020, he presented 2-weeks history of progressively worsening convulsion, and described it as rigidity in his body and drop afterward. Following convulsion, he vomited in projectile description, suggesting an intracranial mass. The complaint did not precede by any other situation or condition. Oncogenic risk factors, such as genetic predisposition, previous head injury, and exposure of oncogenic agent (pesticide, rubber, radiation, and smoke) were not found in this patient.

Physical examination demonstrated somnolence sensorium with Glasgow Comma Scale Score of 12 (E4M4V4), blood pressure of 150/90 mmHg, weakness on left extremities, and right temporal craniotomy scar. Patient arrived at the hospital with the Karnofsky Performance Status Scale of 40. This study was performed preoperative contrast-enhanced brain magnetic resonance

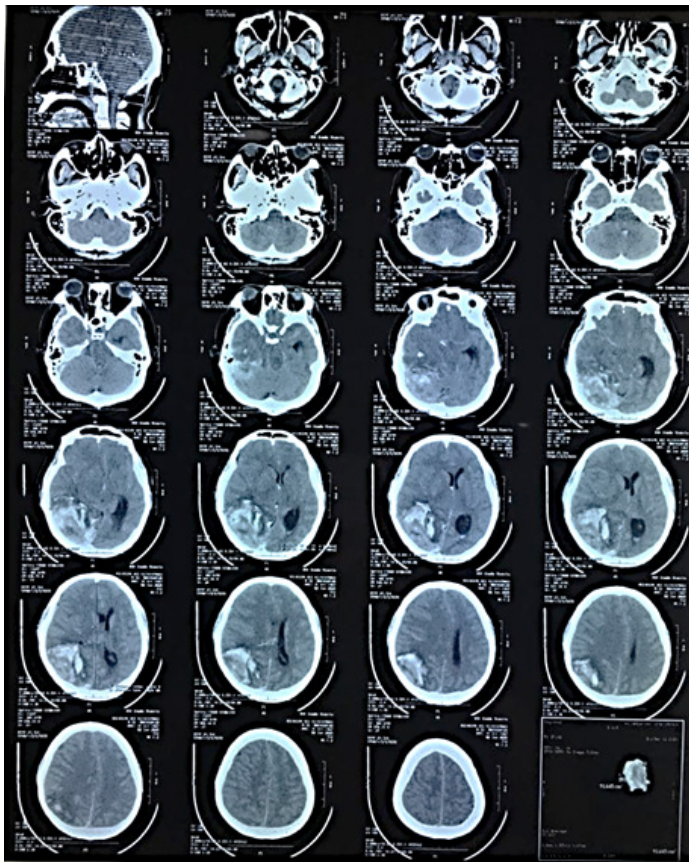

Fig. 1 Head CT Scan Showed An Intracranial Hemorrhage in Right Parietooccipital Region with Midline Shift

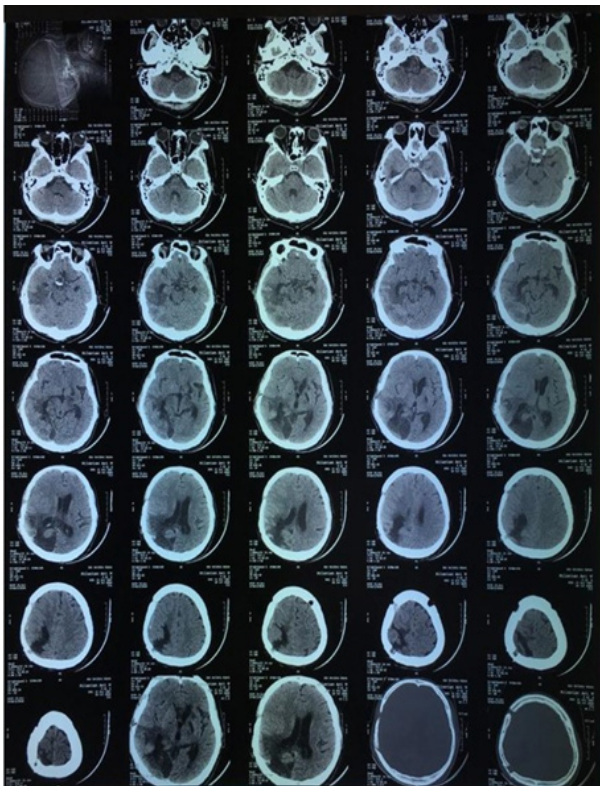

Fig. 2 Follow up Head CT Scan Showed Post Right Parietal Decompressive Craniotomy with Normal Brain Imaging Finding

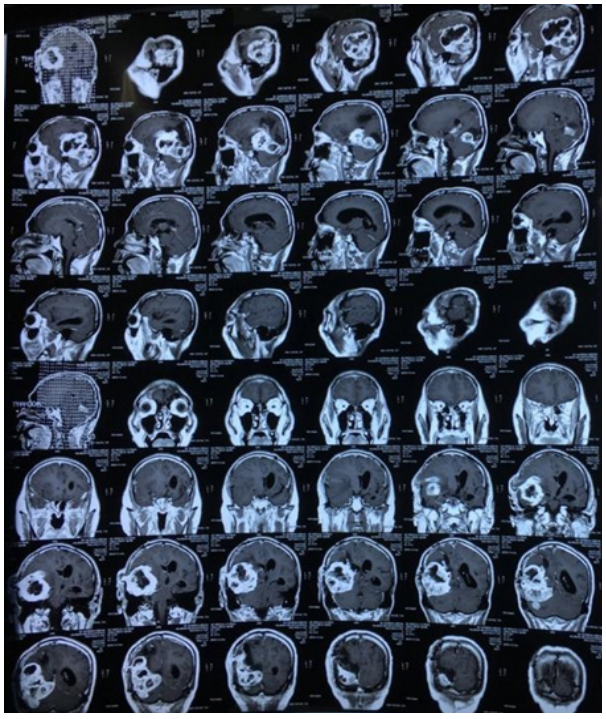

Fig. 3 Preoperative MRI Showed Cerebral Tumor on the Right Temporoparietooccipital Region that Extend to Right Cerebellum with Extracranial Protrusion from Craniotomy Remnant

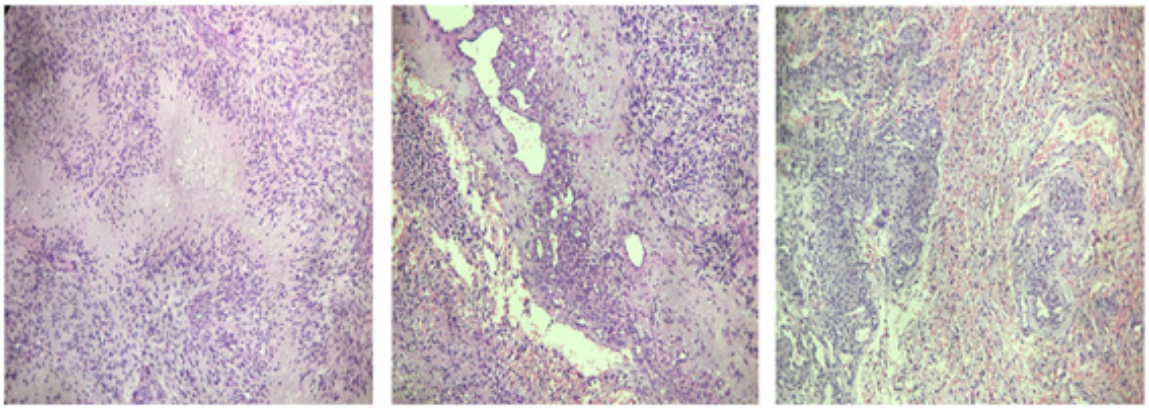

Fig. 4 Histopathological Appearance of the Resected Specimens Showed the Palisading Necrosis (a) Garland pattern of microvascular proliferation; (b) and glomeruloid pattern of microvascular proliferation; (c) Magnification 100X, HE staining

imaging (MRI). The radiological examination demonstrated a 6.8 × 7.1 x 8.6 cm cystic right temporoparietooccipital lesion. The lesion was surrounded by area of heterogeneous contrast enhancement extending to the right corona radiata and periventricular white matter that is associated with cerebral edema (Fig. 3). Furthermore, a mass extension to right brain stem was found.

Craniotomy tumor removal procedure was performed at supine position. Surgery was performed with incision in the previous surgical site. After opening the dura mater and bleeding control, the tumor was then removed by using piecemeal manner. The tumor removal procedure was completed but not all the tumor mass was technically resectable due to the brain stem tumor extension. The tumor had characteristic of cystic, grey and black in color, and can be suctioned during operation. The patient was hemodynamically stable during the surgery and transferred to intensive care unit for post-operative care. His condition improved post-operatively and later he was discharged from hospital. The biopsy specimen was sent for histopathology examination. Histopathological examination concluded that the brain tumor was glioblastoma with microvascular proliferation and palisading necrosis (Fig. 4).

Discussion

Epidemiological studies showed increased brain tumor incidence in previously stroke or head injury patients. Previously stroke patients could increase brain tumor development risk.[7] Ruptured blood vessels in hemorrhagic stroke result in decrease in cerebral blood flow, a mechanism for reducing bleeding, and if the hypoperfusion persists beyond several minutes, brain ischemia arises and brain cells hypoxia ensues.[8] Hypoxic condition may induce brain mesenchymal cells changes into glioma cells.[9] Ngb overexpression promoted the proliferation of neural progenitor cells (NPC), enhanced neuronal differentiation of cultured NPC under differentiation conditions, promotes neurogenesis in mice brain after stroke.[10] GBM can also considered to be developed after infarction that could possibly arising from glial scar. Hence, reactive gliosis may lead to brain tumor development, as GBM proposed to be originated from glial progenitor cells and reactive astrocytes, a type of neuroglia.[11]

When brain undergo hypoxia, neuroglobin (Ngb) is expressed by neuronal and neuroglial cells in order to increase brain cells survival.[1] Ngb, the heme-containing protein, is involved in metabolism of reactive nitrogen and oxygen species as well as in intracellular signaling pathways.[12] In cultured neural (HN33) cells lentiviral vector-mediated overexpression of the hypoxia inducible factor (HIF-1α) subunit, increased expression of HIF-1α was associated with an ~2-fold increase in the expression of Ngb.[13] VEGF and EPO contribute to hypoxia-induced Ngb up-regulation. In cortical neuron cultures, administration of VEGF increased Ngb protein expression however Ngb overexpression in turn suppressed VEGF

expression.[14] This may explain the palisading necrosis and microvascular proliferation in GBM histopathological examination (Fig. 4).

The Ngb expression also increased in human glioblastoma cells during hypoxia *in vitro*.[10] Furthermore, Ngb increase tumor survival capability via Ngb ability to enhance proliferation and inhibit apoptosis by regulating phosphatidylinositol 3-kinase (PI3K)/AKT pathway. The roles of PI3K/AKT pathway in cell proliferation, apoptosis resistance, and cell cycle progression of glioma cells, includes mTOR, Bax, cyclin D1, Bcl-2, and Bcl-2-like 1. mTOR promotes cell survival and proliferation in glioma cells. Altered expression of Bcl-2/Bax has an association with altered levels of glioma cells apoptosis.[9]

In cultured mouse astrocytes, Ngb blocks the stimulation of Bax (pro-apoptotic) and the inhibition of Bcl-2 (anti-apoptotic) expression induced by oxidative stress, and subsequently eliminates caspase 3 activation.[15] Astrocytes have the capabilities to mount antioxidative responses that allow astrocytes to cope with an ischemic environment. Ischemic condition then could activate astrocytes ischemic tolerance that further reduce future ischemic episodes damage from sub threshold ischemic insults. Area of focal brain hypoxia correlates with area of infarction that could be due to impaired reactive oxygen species elimination that result from lack of vimentin and glial fibrillary acidic protein (GFAP). GFAP upregulation indicates astrocytes reactivity found in vast neuropathology conditions such as stroke, neurotrauma, brain tumor, perinatal asphyxia, epilepsy, Parkinson's disease, Alzheimer's disease, or multiple sclerosis.[11] In an injured brain, glial cells express *glial cell-derived neurotrophic factor* (GDNF) *de novo*. In addition, neuroinflammation has been reported to induce GDNF expression in activated astrocytes and microglia, infiltrating macrophages, nestin-positive reactive astrocytes, and neuron/glia (NG2) positive microglia-like cells.[16] The potential of Ngb in astrocytes proliferation remains unclear. After brain injury, reactive astrogliosis showed molecules expression changes and astrocytes hypertrophy proliferation. Therefore, tissue damage and inflammation results in areas of glial scar, proliferating astrocytes, fibromeningeal cells and other glial cells, as well as collagen deposition in extracellular matrix.[17]

In conclusion, GBM case preceding hemorrhagic stroke is rarely reported and hard to be diagnosed. In this case report study, GBM diagnosis in this patient was confirmed by histopathological examination postoperatively.

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