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Radiologic Evaluation of Patients with Glioblastoma Multiforme who Initially Presented with Ischemic Stroke: A Case Series

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Abstract **Background:** Glioblastoma multiform (GBM) is the most common primary brain tumor. Few studies have described the clinical and radiological aspects of GBMs in which initial manifestation mimics vaso-occlusive diseases and transient ischemic attacks (TIAs). In this study, we have described 10 patients with GBM who initially presented with ischemic attacks. **Case Description:** From August 2008 to June 2016, 332 patients with confirmed GBM by histopathological study were referred to Shohada Tajrish Hospital. Of this population, 10 cases initially presented with isolated acute ischemic/vaso-occlusive symptoms and TIA episodes. All of the patients underwent imaging and surgical procedures with confirmed histopathological diagnosis of GBM. **Conclusions:** GBMs involving fronto-temporal and temporal lobes may compress and invade MCA branches and cause acute ischemic stroke as their initial manifestation. Although rare, GBMs should be considered in differential diagnosis in patients with no obvious atherosclerotic risk factors who present with ischemic stroke.

Keywords: *glioblastoma multiforme, initial presentation, transient ischemic attack, imaging, middle cerebral artery*

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1. Introduction

Glioblastoma multiform (GBM) is the most common primary brain tumor, with high infiltrating and angiogenic nature. [1] This WHO grade IV tumor mainly affects individuals in their 5th decade, with male to female ratio of 2:1. [2] Although most of these tumors may originate de novo, malignant transformation from low grade gliomas is responsible for about 40% of these neoplasms. [3] Genetic susceptibility, N-nitroso compound exposure and following traumatic brain injury or cerebral artery infarct has been described as potential etiologic factors. [4] Based on the location, they often cause neurological symptoms such as headache and cognitive dysfunction, followed by seizures and focal neurological deficits. [5] Few studies have described the clinical and radiological aspects of GBMs in which initial manifestation mimics vaso-occlusive diseases and transient ischemic attacks (TIAs). [6] In this study, we describe the radiological features of 10 patients with GBM who presented initially with ischemic vaso-occlusive and TIA symptoms.

2. Case Reports

From August 2008 to June 2016, 332 patients with confirmed GBM by histopathological study were referred to Shohada Tajrish Hospital. Of this population, 10 cases initially presented with isolated acute ischemic/vaso-occlusive symptoms and TIA episodes. Four patients presented with hemiparesis, which one of them progressed to hemiplegia. Two patients experienced hemisensory deficits. Facial weakness and vertigo were observed in 2 cases. Also, speech disorders as dysarthria and aphasia were observed in 2 patients. (Table 1) All patients Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) and Compute Tomography Angiography (CTA) study. Peri-tumoral hypodensity and edema was observed in CT scan of all 10 patients, suggesting ischemic stroke. In addition, MRI study revealed an enhancing heterogeneous mass mostly in fronto-temporal lobe, followed by temporal, parieto-temporal and brain stem areas in all of the patients. These lesions have hypointense signal in T1, hyperintense signal in both T2 and T2/Fluid-attenuated inversion recovery (FLAIR) and high signal intensity in diffusion weighted imaging (DWI) MRI. (Figure 1) Also, CTA with contrast showed complete vessel occlusion in 6 patients. Tumor debulking performed via craniotomy in 9 patients with accessible tumors, except one case with brain stem glioma who underwent chemotherapy with temozolomide and carboplatin and radiotherapy. Specimen of the tumor was sent for histopathological study following open surgery in 9 patients and stereotactic biopsy of the patient with brain stem glioma. Histopathological examination with hematoxylin and eosin (H & E) and immunohistochemistry (IHC) study

with glial fibrillary acidic protein (GFAP) of all specimens confirmed the diagnosis of GBM. In addition, vessel wall infiltration by glial cells and subsequent hematoma formation was observed in all of the specimens. (Figure 2) Written informed consents were obtained from the patients with ethical approval by Ethics Committee of Shohada Tajrish Hospital under the principles of the Helsinki Declaration.

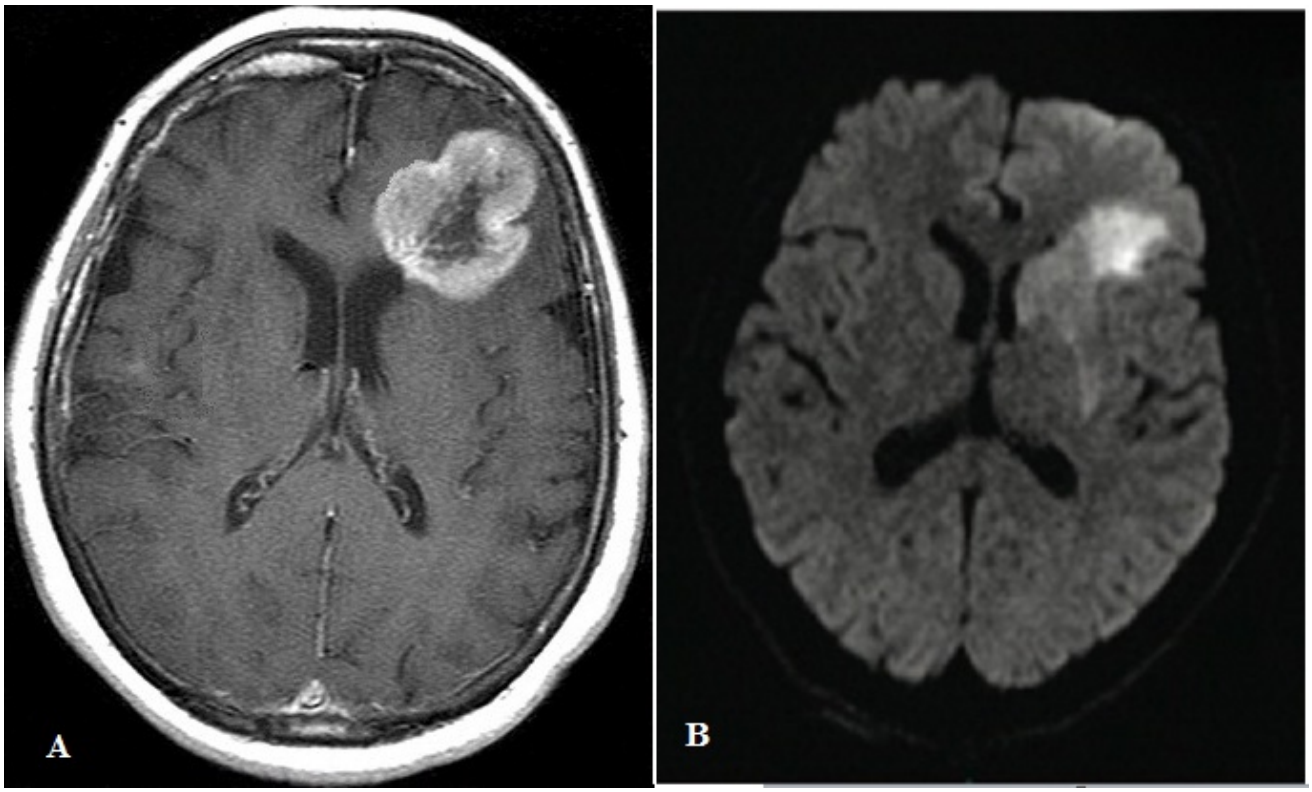

Figure 1. A: T1-weighted MRI shows enhanced lesion with peripheral edema on left frontal area, compatible with high grade glioma. **B:** Left frontal area of same patient has hyper intense signal in diffusion weighted imaging (DWI), compatible with ischemic area

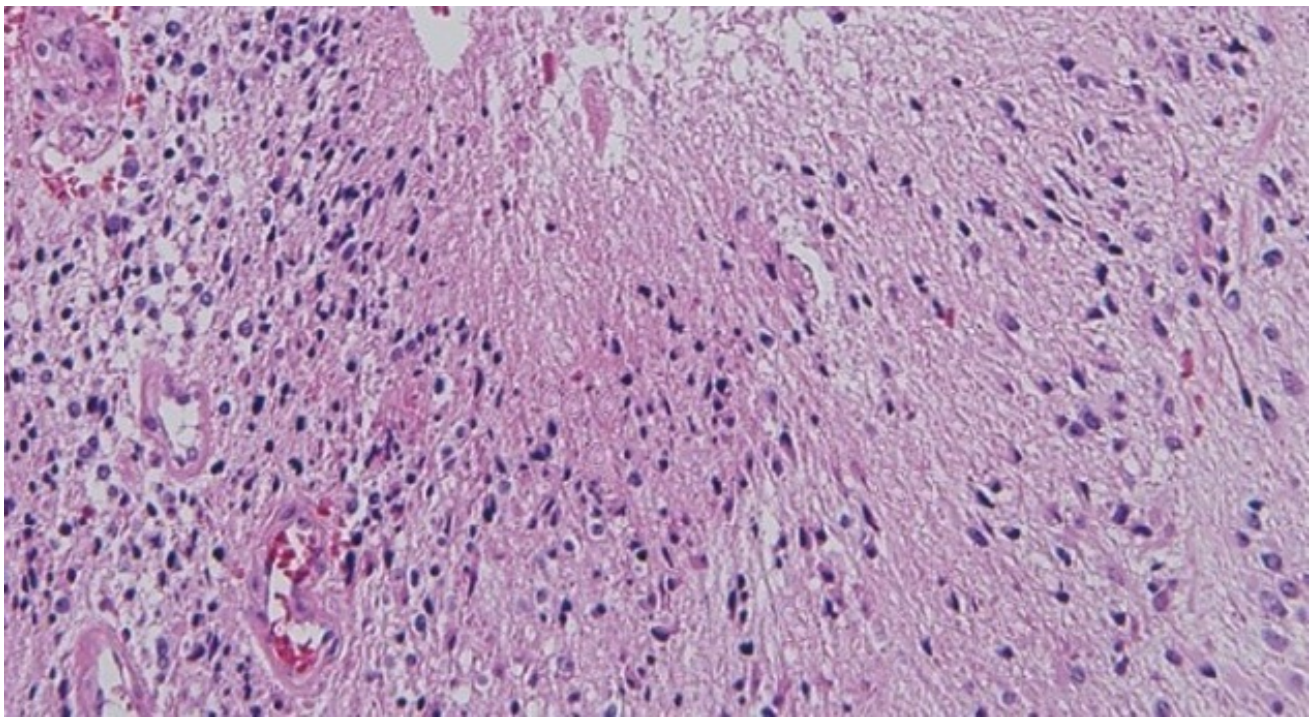

Figure 2. Histopathological examination with hematoxylin and eosin shows atypical pleomorphic nuclear appearance, microvascular proliferation and necrosis along with pseudopalisading feature, compatible with diagnosis of GBM

Table 1.

Case	Age	Sex	Tumor Location	Initial Presentation	Artery Territory	Vessel Occlusion
Number 1	53	Female	Left fronto-temporal	Hemisensory deficit	MCA	Complete
Number 2	61	Male	Right lateral medulla	Vertigo	Basilar artery	Partial
Number 3	57	Male	Right temporo-parietal	Dysarthria	MCA	Partial
Number 4	59	Female	Right lenticulo-capsular	Hemipresis	MCA	Partial
Number 5	72	Male	Left fronto-temporal	Hemipresis	MCA	Complete
Number 6	48	Male	Left parietal	Facial weakness	MCA	Partial
Number 7	67	Male	Right temporal	Aphasia	MCA	Complete
Number 8	55	Female	Left frontal	Hemiparesis	MCA	Partial
Number 9	76	Female	Right fronto-temporal	Hemisensory deficit	MCA	Partial
Number 10	54	Male	Right temporo-parietal	Hemiparesis	MCA	Partial

MCA: Middle Cerebral Artery.

3. Discussion

GBMs originate from glial cells or their precursors in central nervous system (CNS) and pose a great challenge both to patient and the clinician, due to their catastrophic prognosis. Majority of patients with primary GBM die within 3 months without treatment. However, surgical resection along with chemoradiotherapy extends their survival rate up to 2 years. [7] They often arise from subcortical white matter of cerebral hemispheres in temporal lobe, followed by parietal, frontal and occipital lobe, and less frequently, brain stem and cerebellum. [8] On CT scans, GBMs appear as an irregular hypodense lesion with peripheral ring enhancement by contrast media. These tumors exhibit characteristic features on MRI, including enhancement on T1-weighted and peripheral edema enhancement on T2-weighted images. Central hypo-intensity and ring enhancement represent necrosis and high concentration of neoplastic cells with abnormal permeable vessels to contrast media, respectively. GBMs tend to spread along the white matter tracts of corpus callosum to invade contra-lateral hemisphere, causing butterfly appearance. Also, heterogeneous signal intensity is caused by multiple foci of cysts, necrosis and hemorrhage. [9,10] Also, GBMS have reduced N-acetyl aspartate (NAA) signal and increased levels of Choline (Cho), leading to increased Cho/NAA in MR spectroscopy study. [11] Histopathological characteristics of GBM have been marked by poorly differentiated pleomorphic cells with increased nuclear to cytoplasmic ratio and elongated coarsely clumped hyperchromic chromatin. Necrosis, cyct formation and microvscular proliferation are among features which give “multiform” name to the tumor. In addition, GFAP remains the most accurate diagnostic marker in comparison to vimentin and fibronectin in IHC study of GBMs. [12] Cerebral neoplasms may cause acute onset of neurological deficits by intracranial hemorrhage. Rarely, sudden neurological symptoms may be attributable to ischemic stroke secondary to CNS malignant tumors. Acute ischemic stroke results from sudden loss of blood supply in cerebral vessels. Irreversible neuronal injury though to begin at blood flow rate less than 18 mL/100g of tissue, leading to multiple types of neurological deficits, based on vascular territory. [13,14] Due to distinct position of meningiomas, these tumors are the most common cerebral neoplasms which have the potential to affect different portions of intracranial vasculature and cause subsequent neurological symptoms. [15] Based on our review of literature, there are few reports describing acute onset of ischemic stroke secondary to malignant gliomas. Aoki et al reported the first case of cerebral infarction caused by direct GBM invasion to vessel wall, resulting in MCA dissection. [16] In 2011, Chen et al described a patient who initially presented with ischemic stroke, which further work ups revealed MCA branches compression by GBM in her left fronto-temporal lobe. [17] In addition, two patients with acute ischemic stroke secondary to GBM by MCA branch compression were reported recently. [18,19] In our series, MCA branches were the most affected vessel (90%) by either direct invasion or compression caused by GBM. Although most of our patients were diagnosed with tumors in their fronto-temporal and temporal lobes, we have described the first reported case of ischemic stroke secondary to brain stem glioma which invades right basilar artery, resulting in vertigo. Moreover, imaging studies revealed partial vessel obstruction by GBM in most of our patients (70%), while complete vessel obstruction was observed in three patients in their fronto-temporal and temporal lobes. There is a debate about whether compressed vessel in tissue specimen belongs to MCA branches or it is the result of tumor angiogenesis. However, it is well known that GBMs often develop more irregular vessels, with different structural patterns than MCA branches. [20] It is hypothesized that low blood flow state attributable to progressive compression of MCA branches by tumor may cause cerebral infarction. [21,22] Author’s assumption of acute ischemic stroke as initial presentation of GBM in all of the cases is supported by the fact that none of our patients had either evidence of significant cervical or peripheral atherosclerosis or previous similar symptoms. In addition, none of our patients had received previous brain radiotherapy and cardio-embolic source were ruled out. Also, patients with potential atherosclerotic risk factors were under acceptable medical control. Due to increased risk of intra-tumoral hemorrhage, recombinant human tissue-type plasminogen activator is not indicated. [23] Treatment in these patients should focus on maximum tumor resection and subsequent chemoradiotherapy. In conclusion, GBMs involving fronto-temporal and temporal lobes may compress and invade MCA branches and cause acute ischemic stroke as their initial manifestation. Although rare, GBMs should be considered in differential diagnosis in patients with no

obvious atherosclerotic risk factors who present with ischemic stroke.

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