

# A Case of Multicentric Gliomatosis Cerebri Diagnosed with Brain Biopsy

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**Background:** Gliomatosis cerebri (GC) is a rare subtype of the CNS glioma and about 300 cases of GC are reported hitherto. Among those cases, multicentric GC was exceedingly uncommon. **Case Report:** A 63-year-old man was admitted with dizziness, nausea, and vomiting. Brain magnetic resonance image showed multiple, non-contiguous brain lesions in corpus callosum, right thalamus, midbrain and frontal and temporal cortices. The 14-3-3 protein was identified temporarily in this patient. Brain biopsy was performed to confirm the diagnosis and anaplastic astrocytoma was found at the right frontal cortex. **Conclusion:** This is the case report of pathologically confirmed GC with multicentric brain lesions. **J Neurocrit Care 2009;2:66-69**

**KEY WORDS:** Gliomatosis cerebri · Multicentric.

## Introduction

Glioma is a type of primary central nervous system (CNS) tumor that arises from glial cells. Although gliomatosis cerebri (GC) is a subtype of the CNS glioma, it is distinct from other tumors of glial origin and classified as neuroepithelial tumor of uncertain origin.<sup>1</sup> Primary GC shows diffuse infiltration of neoplastic glial cells through more than two cerebral lobes or the infratentorial structures in the absence of any identifiable tumor mass.<sup>2</sup> Because neoplastic cells infiltrate the cerebral lobes with relatively mild destruction of the architecture of normal surrounding tissues, clinical symptoms of GC might be very subtle in contrast to its radiological findings.<sup>3,4</sup> The GC has non-specific clinical presentations such as headache, seizure, memory impairment, confusion, unsteady gait, nausea, dizziness and vomiting.<sup>3,4</sup> GC is a rare disease and multicentric GC was exceedingly uncommon among hundreds of reported cases with GC.<sup>5</sup> We report a case of non-contiguous GC confirmed with the brain biopsy.

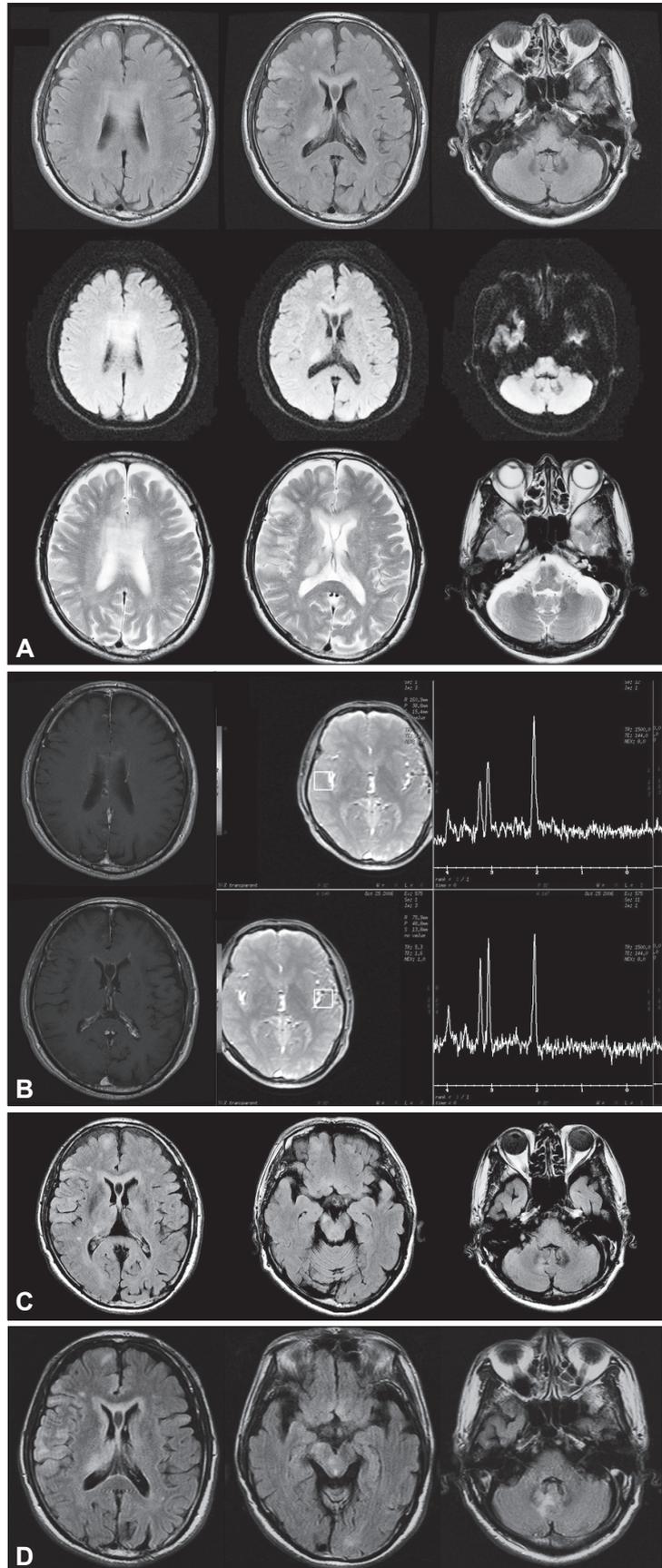
## Case

A 63-year-old man was admitted with dizziness, nausea,

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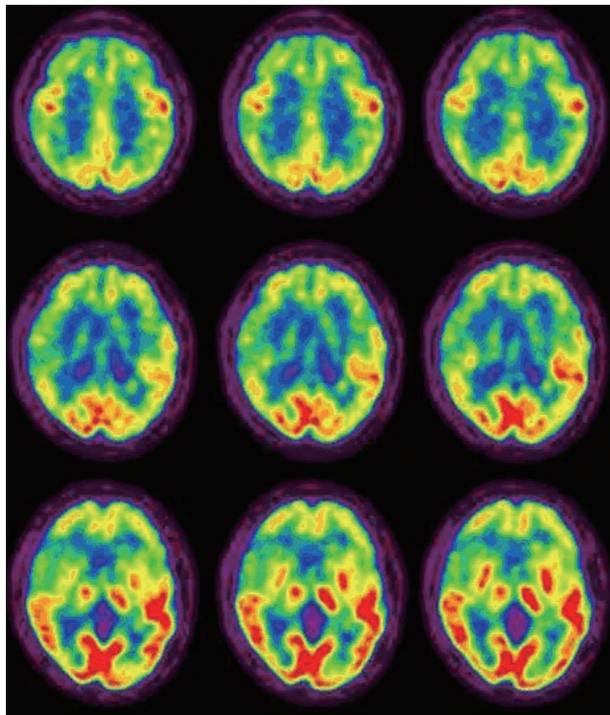
and vomiting for 2 weeks. He was a 40-pack-year smoker and did not have any past surgical or medical history. Initial vital signs were stable and within normal limit, and physical exam was also normal. Neurological examination showed mild dysarthria and bilateral sway on tandem gait. Other neurological exam including extraocular movement was normal. Routine laboratory tests including CBC, LFT, TFT, and autoimmune studies showed normal results. Tumor markers (AFP, CEA, PSA, CA19-9) and paraneoplastic autoantibody test (Hu antibody, Ri antibody, Yo antibody, antinuclear antibody) were all negative. Brain magnetic resonance image (MRI) showed multiple scattered lesions in corpus callosum, right thalamus, right midbrain, and right frontal and temporal cortices (Fig. 1A). Contrast enhanced brain MRI and MR spectrography (MRS) was carried out at three weeks after the onset of symptoms. Same lesions were found with iso-intensity signal on T1 weighted images and were not enhanced (Fig. 1B). On MRS, choline (Cho)/creatinine (Cr) and choline/N-acetylaspartate (NAA) ratio was not significantly different between bilateral temporal cortices. Routine CSF study and microbiologic markers were all normal, but, 14-3-3 protein was positive. On electroencephalogram (EEG), posterior dominant rhythm was well regulated with 8 Hz activity, and there was no epileptiform discharge, periodic complexes or focal slowing. Neuropsychological (NP) test demonstrated preserved higher cortical functions except naming (Korean Boston naming test: 8 percentile).

Neither dizziness nor dysarthria was improved significantly



**FIGURE 1.** MRI findings of the patient as time interval. A: Initial brain MRI showed increased signal intensities in right thalamus, right midbrain, right frontal and temporal cortices, and corpus callosum on T2WI and FLAIR images and increased signal intensities at corpus callosum and right thalamus on diffusion images. B: Contrast enhanced brain MRI and MR spectrography (MRS) at three weeks after the onset of symptoms showed same lesions with iso-intensity signals on T1 weighted image without enhancement. C: Follow-up MRI at three months after the onset of the symptoms showed increased size of previous lesions and a newly developed lesion at right cerebellar vermis. D: Follow-up MRI at five months after onset of first symptom showed enlarged cerebellar lesion.

with steroid pulse therapy. Instead, nausea and vomiting disappeared with digestives and GI motility drugs for following two months. After then, dizziness, nausea and vomiting disturbed the daily activities of the patient again. Follow-up MRI at three months after the onset of the symptoms showed increased size of previous lesions and a newly developed lesion at right cerebellar vermis (Fig. 1C). Brain and whole body positron emission tomography (PET) was performed to rule out the underlying malignancy. However, it showed no abnormal glucose metabolism except decreased glucose metabolism at bilateral frontal and parietal lobes (Fig. 2). Follow-up EEG was normal and 14-3-3 protein of CSF became negative for two times. IgG index was 0.51 and oligoclonal band was negative. Gait and truncal ataxia became prominent at 5 months



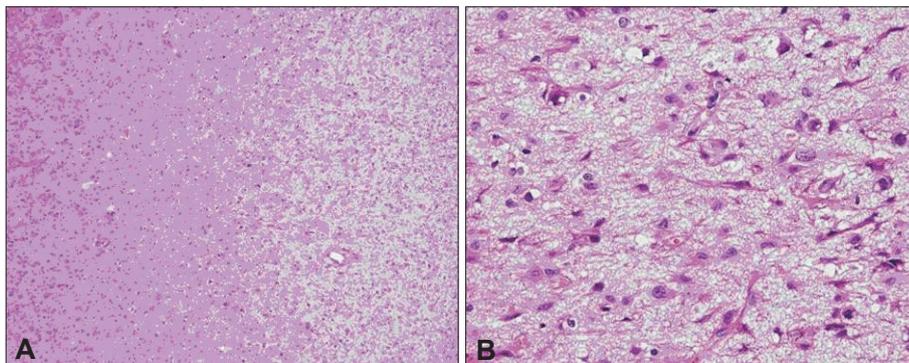
**FIGURE 2.** Brain PET scan showed mildly decreased glucose metabolism on bilateral frontoparietal cortex. Bilateral BG, thalamus and cerebellum showed symmetric glucose metabolism.

after the onset of first symptoms and follow-up MRI showed enlarged cerebellar lesion (Fig. 1D). We performed the brain biopsy on right frontal cortex and anaplastic astrocytoma was found (Fig. 3). After the biopsy, mental status of the patient became comatose without additional focal neurological deficit. Further brain imaging and anti-cancer treatment were refused by the family members. The patient died at three weeks after the biopsy.

## Discussion

Clinical symptoms or radiological features of primary GC are non-specific and patients are often misdiagnosed with other neurological disease such as CNS inflammatory disease, arteriopathies or leukoencephalopathies.<sup>5</sup> MRI using contrast media generally provides important information for the diagnosis of brain tumor and contrast enhancement means the breakdown of blood-brain barrier, which is often associated with high grade tumor. However, it was reported that about 80% of patients with GC showed no contrast enhancing lesions on T1WI despite its malignancy.<sup>5</sup> It was also true in our patient; initial symptoms of the patient were non-specific and there was no mass lesion with prominent contrast enhancement. Subsequently, the next non-invasive diagnostic methods could be MRS, in which malignant GC demonstrates elevated ratio of Choline/NAA<sup>6</sup> and FDG-PET scan, in which high grade brain tumors generally show increased glucose metabolism.<sup>7</sup> However, in our case, the ratio of Choline/NAA was not elevated on MRS and there was no difference of glucose metabolism in the abnormal lesion on PET scan. Furthermore, unlike other GC, our case has multicentric brain lesions; diffuse infiltrations at corpus callosum, right thalamus, midbrain and distant focal lesions of frontal and temporal cortices. Those results made it difficult to diagnose properly without the brain biopsy.

Multiple gliomas are well-recognized but uncommon entity. They are grouped in two categories: multifocal and multicentric gliomas. Multifocal gliomas disseminate along an es-



**FIGURE 3.** Photomicrography of the biopsy specimen from the right frontal cortex. A: The tumor cells are diffusely infiltrative with high cellularity and produce little destruction of preexisting parenchyma. H&E stain,  $\times 40$ . B: It composed of fibrillary glial cells that resemble astrocytes with nuclear atypia. Mitoses are generally infrequent and vascular proliferation and necrosis is absent. H&E stain,  $\times 200$ .

established route, spreading through commissural pathways, CSF channels, blood or by local extension through satellite formations; multicentric gliomas are separated lesions that cannot be attributed to one of the above pathways.<sup>8,9</sup> There are two different hypotheses regarding widespread nature of GC, i.e., 1) GC arises from simultaneous neoplastic transformation of cells in different regions of the brain (oligoclonal origin hypothesis) by stimulation of specific intrinsic or extrinsic<sup>10,11</sup> carcinogenic influences or 2) GC arises from a single clone of cells and then spreads widely (monoclonal origin hypothesis).<sup>4</sup> Although the MRI of our case was compatible with multicentric glioma/oligoclonal origin hypothesis, PET findings suggested the involvement of bilateral frontal and parietal cortices. It is possible that there were underlying neoplastic cell infiltration without MRI signal changes.

Despite the 14-3-3 protein assay has proved useful in the diagnosis of Creutzfeldt-Jakob disease (CJD) with average sensitivity and specificity of 92%,<sup>12,13</sup> it can be found in the patients with astrocytoma, herpes simplex encephalitis, hypoxic brain damage, atypical encephalitis, intracerebral metastases of a bronchial carcinoma, metabolic encephalopathy, and progressive dementia of unknown cause.<sup>14</sup> Then, it is recommended to perform the test twice and if contradictory, a third test must be done to establish a final result.<sup>13</sup> In this case, the pathology of anaplastic astrocytoma made the false positive result in 14-3-3 protein assay and third test established the negative result.

GC showed fatal outcomes and overall median survival was 14.5 months in the 296 cases of GC with treatment.<sup>5</sup> Radiotherapy was reported to improve clinical symptoms, but it usually had minimal effect on patients' survival. However, recent randomized controlled trial performed in patients with glioblastoma has showed a survival benefit with concomitant and adjuvant temozolomide added to conventional radiotherapy. In this study, the 5 year-survival rate was 10% in the patients with temozolomide plus radiotherapy versus 2% in the patients with radiotherapy alone.<sup>15</sup> This result can be applied in patients with GC.

Our case was compatible with the GC in that multiple lobe invasions were confirmed with radiological findings and anaplastic astrocytoma was confirmed with the brain biopsy. Al-

though many studied other than biopsy might be helpful in part, we suggest that pathological confirm should be required for the diagnosis of GC.

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