Acquired Glioblastoma Following Prior Middle Cerebral Artery Infarct: Case Report and Literature Review

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Abstract

A 79-year-old woman presented with an acute onset of right-sided hemiplegia and global aphasia. Neuroimaging revealed an occlusion of the initial M1 segment of the left middle cerebral artery. Six years later, the patient presented with a necrotic, strongly enhancing tumor with mass effect locating in the area of the previous infarction. An open biopsy with histological examination showed a typical glioblastoma multiforme. Based on the recent molecular analyses coupling with stem cell theory, we discuss possible mechanisms involving in the neoplastic transformation from infarcted brain with review of the literature.

Keywords: Cerebral Infarction; Glioblastoma; Neoplastic Transformation

Introduction

There is no clear evidence regarding causative relationship between stroke and brain tumor so far. Generally, intracranial tumors may present with sudden onset of stroke-like symptoms, which sometimes are misdiagnosed as ischemic stroke. The most common intracranial tumors masquerading as acute stroke are the malignant gliomas, meningiomas, and metastases [1,2]. In addition, there are few reports of low-grade gliomas presenting as a stroke initially, which can later transform to high-grade gliomas [1,3]. Rarely, the co-existence of two separate disease processes, a brain tumor and an ischemic stroke resulting from atherosclerosis, may lead to coincidental symptom production [4]. No matter what the nature of the tumor, patients with brain tumors usually present with progressive focal neurological deficit and increased intracranial pressure, which often lead to accurate diagnosis by subsequent radiographic examination.

In contrast, the incidence of a primary brain tumor in an area of cerebral infarction is thought to be extremely rare. No epidemiological studies could be found in the literature investigating the risk for malignant astrocytic tumors after cerebral ischemic infarction. Previous reports have suggested that the severe head injury is a significant risk factor for the development of glioblastoma multiforme (GBM) with a latency period of at least one year after injury [5,6]. Here, we present a patient who developed GBM six years after an ischemic stroke. We analyzed the potential association between cerebral ischemic infarction and the subsequent risk for developing a malignant glioma based on the existing evidence of neoplastic transformation from posttraumatic brain.

Case Presentation

Initial Medical History

In 2008, a 79-year-old woman with a history of the coronary heart disease and atrial fibrillation under control with medical treatment, had an acute onset of right hemiplegia and then lost consciousness. Head computed tomography (CT) revealed multiple lacunar infarction in the bilateral basal ganglia, with a high-density in the left MCA (Figure 1a), which was highly implicative of occlusion of the left MCA. The patient recovered consciousness on the third day, presenting with right-sided hemiplegia and...
global aphasia after anticoagulant therapy with antiplatelet agent. Repeated CT scan clearly revealed a developing left MCA infarct area including the left frontal, temporal, parietal lobes and basal ganglia, accompanied with moderate sinistrocerebral edema and narrowing of the left cisterna ambiens (Figure 1b). Magnetic resonance angiography (MRA) report suggested an occlusion of the initial M1 segment of the left MCA (imaging not available). Despite of intravenous thrombolysis with urokinase, the patient still suffered motor aphasia and right hemiplegia. Finally, she was discharged for further rehabilitation.

**Follow-Up Neurological Imaging**

The patient’s neurological status remained stable through regular follow-up examination. Three years later, repeated head CT revealed a well-defined area of encephalomalacia foci in the left MCA distribution accompanied by compensatory dilation of the left lateral ventricle (Figure 2a). There was no evidence of mass effect on the non-enhanced CT examination four years after the first stroke, with extensive glial scar formation in the territory of previous infarction (Figure 2b).

**Clinical Features of Mass Lesion**

At the end of 2014, the patient was admitted to our hospital again, due to the persistent headache, vomiting and anorexia associated with deteriorating state of consciousness for one week. An emergency CT scan revealed a large, heterogeneous density locating in the previously MCA infarcted area (Figure 2c). Later, a contrast-enhanced MRI showed a necrotic, strongly enhancing tumor with mass effect, extending from the left frontal lobe to the temporal and parietal lobes, which was thought to originate from the scar of the cerebral infarction (Figure 2d). A decision was made in coordination with the family’s consent to undergo a drilling biopsy to confirm the pathologic diagnosis. Histologic diagnosis was GBM with many astroblast formations. However, the immediate

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**Figure 2: Development of glial scar and formation of the GMB after ischemic stroke.**

A. CT without contrast 36 months after ischemic stroke, showing a glial scar without space-occupying effect.
B. CT scan 48 months after ischemic stroke, showing expansion of the ipsilateral ventricles due to the contracture of the glial scar.
C. CT without contrast 6 years after ischemic stroke, showing a dense, cystic lesion in the left frontal, temporal, and parietal lobes, corresponding to the region of the pre-existing infarct.
D. MRI T1 sequence after gadolinium contrast showing irregular enhanced, large mixed intensity lesion at the site of the previous infarcted territory.
radiotherapy and chemotherapy were not implemented due to her worsening condition. Her family chose symptomatic treatment and palliative care for her. She died four weeks after the diagnosis of GBM.

Pathologic Analysis

Histological examination revealed pleomorphic neoplastic cells with irregular hyperchromatic nuclei, multiple atypical mitoses, and disorganized astroblast formations. Atypical vascular proliferation and pseudopalisading necrosis were also prominent. These features were consistent with GBM (Figure 3). Immunostaining was strongly positive for Ki67 in approximately 25%-30% of cell nuclei.

Discussion

Intracranial tumors derived from damaged brain are rare, and are more often related to benign tumors, such as meningiomas and lower-grade astrocytomas [5]. To our knowledge, there are only a few reports of glioblastoma associating with ischemic strokes [7,8]. Given the underlying pathological mechanism is unclear, most authors have attributed it to either misdiagnosis of brain tumor as stroke [2,9,10] or physiologic responses to tumor growth [11,12]. Thus, the discrimination between brain tumors mimicking stroke and a true ischemic stroke is crucial to avoid improper treatment. There was only 3–5% of brain tumors being initially misdiagnosed as stroke in the literature [2,11]. These tumors often show hypo-dense shadow on enhanced CT scan without evidence of mass effect, masquerading as acute stroke. However, they are easily detected on post-contrast MRI examination after few months [13]. Additionally, glioma cells are able to invade and weaken vascular walls, leading to direct occlusion or vascular dissection causing acute cerebral infarct in the corresponding arterial territory, which is likely to be suddenly worsening of the patient’s clinical status [10,11,14].

On contrary, the cause of the ischemic stroke in our case was an embolism of MCA by cardiac emboli, and we do not exclude possible vascular compression or invasion by a previously existed tumor. Given that 90–95% of grade IV astrocytic tumors arises de novo, hence without precursor lesions [15]. If any GBM had been present at the site and the time of initial stroke, she would not have been asymptomatic for more than six years, because these tumors grew so rapidly that the longest survival time in patients up to 70 years without surgical treatment was less than two years reported in the population-based cohort study [16]. Based on case reports and radiological study, it has been speculated that some low-grade lesions (WHO grades I-II astrocytic tumors) may present as a stroke initially, which can later transform to grade III or IV tumors [1,3,17]. This is a normal process that occurs by way of ischemic stimuli, tumors can hijack the machinery to promote growth and invasiveness, characterizing by neovascularization [3]. In fact, most of low-grade tumors confine them to a linear growth model for years due to lack of vascularization, whereas the hypervascularization present in GBM allows for exponential growth and subsequent rapid clinical decline [3,7,17]. Therefore, it is hard to imagine that a preexisting low-grade tumor locating in the large area of the previous infarction would subsequently transform to GMB without enough nutrients provided by circulating blood.

The mechanism of primary brain tumor occurrence in the hypoxic-ischemic injured brain is incompletely understood. Studies on the neuronal regeneration after injury of the central nervous system (CNS) provide new insight into the cellular origin of posttraumatic human glioma. Ischemic and traumatic injuries of the CNS inducing reactive astroglialosis seem to play a significant but contradictory role during regeneration and recovery [18-20]. These cells release growth factors and cytokines, which are also expressed by GBM and other cancers are likely to prevent cell death and modulate activation of neural stem cells/progenitor cells in the brain [19,21,22]. Consequently, the activated stem cells/progenitor cells are capable of some characteristic of gliomas, including high mitotic activity, association with possession of the same antigenic phenotypes as the normal host cells [5,18,23,24]. However, whether a normal stem/progenitor cell differentiates into a mature neuron and astrocyte or becomes a so-called tumor stem cell, depending on a delicate interactions regulated by different growth genes, tumor-suppressing genes and signaling pathways oriented to cell differentiation [20,25]. It is possible that the excessive activation of growth genes and inactivation of tumor-suppressing genes under the pathological conditions could induce gene mutation or convert the stem/progenitor cells into premalignant astrocytes, which may have developed into malignant gliomas. Since the astrocytic response to stroke is extremely complex, there may be other microenvironment factors involving in the pathological process of glioma formation.

In theory, any type of damage to the brain parenchyma may increase the long-term risk specifically for astrocytic

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tumors. However, epidemiological studies failed to find any correlation between the incidence of malignant glioma and ischemic strokes or other structural brain injury [5,6,12]. The possible reasons are as follows: first, most patients with asymptomatic brain damage (eg, mild concussion, lacunar infarction and other degenerative diseases) are not been recognized until the brain tumor diagnosis, which make it difficult to confirm the cause and effect between the two parameters. Second, some small white matter diseases are not clinically considered as the precipitating factors for tumor genesis; with the majority of elderly individuals (> 60 years old) presenting with different degrees of white matter abnormality and/or multiple lacunar infarction [26]. Just as a large area cerebral infarction appears to have led to GBM development in our case, we speculate that an uninterrupted reactive astroglia following the multiple ischemic lesions could increase a chance for a stem/progenitor cell to undergo neoplastic transformation, which can explain why the malignant brain glioma are more common in elderly patients than in young adults [27]. In line with a reverse causality interpretation, however, Munch et al. [6] advocated that enhanced immunoreactions, astroglialysis, as well as other inhibitory molecules responding to brain injury, could be strong enough to suppress or clear premalignant astrocytes and stem/progenitor cells, and hence reduction of the neoplastic transformation, although these inflammatory responses are not conducive to the CNS regeneration after ischemic and traumatic injuries. Actually, most of malignant astrocytic tumors initially occur without precursor lesions, suggesting that brain tumors may originate from other cellular origins in addition to the astrocytic origins, and therefore are likely to have different etiologies.

Although speculative, as an exceptional case, it may sound reasonable for malignant gliomas to originate from reactive astroglia following the damaged brain, based on available evidence that the brain parenchymatous injury accelerates proliferation of astrocytic cells and differentiation of stem/progenitor cells [17,19,28]. Without sequentially tissue samples from different stages of the malignant transformation, the hypothesized mechanisms of inflammation-associated tumor genesis remain conjectural. Further studies on the long-term risk for the development of malignant brain tumors from ischemic infarction are indispensable to provide important information regarding the fundamental mechanisms involved during the initiation, proliferation, and evolution of these tumors.

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