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Glioblastoma arising within sites of encephalomalacia from cerebrovascular insult: two cases and a review of the literature

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ABSTRACT

Glioblastoma is the most common primary parenchymal brain malignancy, with median survival of less than one year. While there are likely multiple predisposing genetic and environmental factors in glioblastoma formation, chronic inflammation resulting from non-traumatic vascular brain injury is one proposed risk factor for oncogenesis. Here, we report two instances of glioblastoma arising within areas of encephalomalacia caused by remote vascular insults (one following aneurysmal subarachnoid hemorrhage and one following ischemic infarction), review the literature associating glioblastoma with prior brain injury, and discuss potential mechanisms for malignant transformation in injured brain tissue.

1. Case reports

1.1. Case 1

A 64-year-old man suffered a subarachnoid hemorrhage from a ruptured anterior communicating artery aneurysm and was treated with surgical clipping (Fig. 1A–C). Aside from secondary epilepsy controlled with levetiracetam, he recovered completely. Six years later, he became withdrawn and confused over two weeks. MRI brain revealed an enhancing left frontal lesion and leptomeningeal enhancement in the region of encephalomalacia related to his prior aneurysmal clipping (Fig. 1D and E). The lesion was resected and histopathology demonstrated glioblastoma, IDH1 wild-type, MGMT unmethylated. The patient was initiated on palliative radiation therapy; however one month after glioblastoma diagnosis, the decision was made to stop treatment as it was not felt that the patient would tolerate temozolamide or further radiation therapy. Hospice services were initiated and no further follow-up was arranged.

1.2. Case 2

A 61-year-old man presented with acute right hemiparesis due to a left middle cerebral artery (MCA) territory infarction (Fig. 2A–C). Seven months later, he developed sudden onset left-sided weakness. MRI brain revealed a new right MCA distribution ischemic stroke as well as a new left parietal enhancing lesion in the territory of his prior stroke (Fig. 2D and E). Pathology of the resected left parietal lesion demonstrated glioblastoma, IDH1-wildtype, MGMT methylated. The patient underwent treatment with temozolamide and radiation. Seven months after glioblastoma diagnosis, the patient was enrolled in a clinical trial due to disease progression. The patient passed away 3 months later, 10 months after GBM diagnosis.

1.3. Summary of cases of glioblastoma preceded by either subarachnoid hemorrhage or ischemic stroke

We identified a total of 16 cases of glioblastoma preceded by subarachnoid hemorrhage (SAH) or ischemic stroke (14 cases identified in the literature and the 2 new cases presented here, Table 1). 7 cases arose after SAH and 9 cases after ischemic stroke. The mean age at tumor diagnosis was 49.9 years (± standard deviation 9.8 years) for the SAH group and 60.9 years (±15.2 years) for the stroke group. The mean duration from vascular event to tumor diagnosis was 5.6 years (±5.7 years) for the SAH cases and 1.5 years (±1.9 years) for the ischemic stroke cases. The tumor developed less than one year from the vascular event in 2 of the 7 SAH cases and 6 of the 9 ischemic stroke cases. Aneurysms involved the internal carotid artery (n = 3), the middle cerebral artery (n = 3), the anterior communicating artery (n = 2), and the anterior cerebral artery (n = 1) (in some cases more than one vessel was involved). Stroke locations were documented as involving the MCA territory

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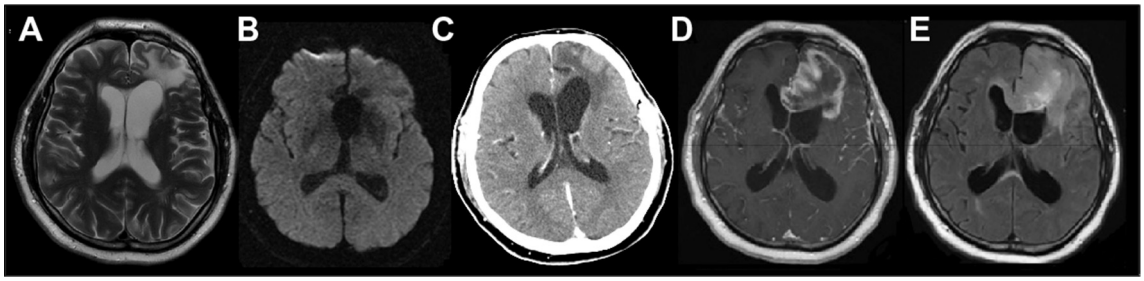

Fig. 1. Case 1: A-C): Imaging 3 years prior to GBM diagnosis. A) T2 sequence showing encephalomalacia in the left frontal lobe 3 years after aneurysmal rupture and clipping and 3 years before GBM diagnosis. B) DWI sequence 3 years before GBM diagnosis. C) Contrast-enhanced CT scan showing no enhancing lesion 3 years prior to GBM diagnosis. D-E): MRI at time of GBM diagnosis. D) T1-contrast enhancement around borders of encephalomalacia, as well as evidence of pachymeningeal and leptomeningeal enhancement. E) FLAIR sequence with edema and encephalomalacia in the left frontal lobe, within area of prior aneurysmal rupture and clipping.

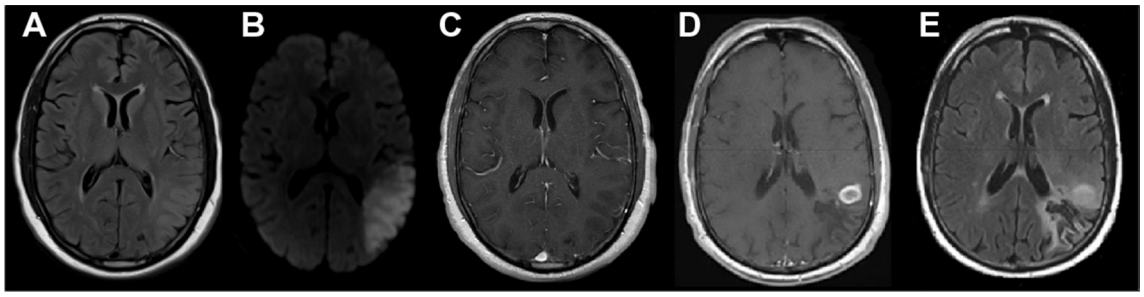

Fig. 2. Case 2. A-C) MRI performed 7 months prior to GBM diagnosis. A) FLAIR sequence demonstrating T2 hyperintensity in the left parietal lobe and posterior temporal lobe consistent with subacute stroke. B) DWI sequence showing wedge-shaped diffusion restriction in the left parietal lobe, consistent with subacute stroke. C) T1 post-contrast sequence showing no enhancing lesion 7 months prior to GBM diagnosis. D-E) MRI performed at time of GBM diagnosis. D) Enhancing lesion on T1-contrast weighted image. E) FLAIR sequence demonstrating area of encephalomalacia from prior stroke where lesion is situated.

(n = 5), frontal (n = 2), temporoparietal (n = 1) and lacunar (n = 1) regions. Pathology specimens from the majority of the tumors were described as glioblastoma multiforme (n = 11).

2. Discussion

2.1. Association between vascular brain injury and glioblastoma: A review of the literature

As early as 1922, Harvey Cushing proposed a causal relationship between head trauma with resultant meningeal scar formation and development of meningiomas [1], however more recent epidemiological studies examining the relationship of brain tumor with preceding traumatic and non-traumatic brain pathology (e.g., cerebrovascular disease) have generated conflicting results [2,3]. A Danish study of 8.2 million people found no significant change in the risk of malignant astrocytic tumors after intracerebral hemorrhage (rate ratio (RR) 1.39, 95% confidence interval (CI) 0.64-2.60), but found a mildly protective effect of ischemic stroke (RR 0.69, CI 0.47-0.96) five or more years after the stroke [2]. Of note, there was a much higher risk of tumor development within the first year after vascular injury (RR 15.3 for ischemic injury [CI 13.5-17.3] and 36.3 for hemorrhagic injury [CI 27.7-46.5]), but these temporally proximal cases were excluded from the main analysis due to their potential for reverse causality or surveillance bias. Alongside these epidemiological findings, there are a number of case reports of high-grade gliomas occurring at sites of prior aneurysmal rupture [4–8] or ischemic stroke [9–15] (mean time interval of 3.3 years between the vascular injury and glioma diagnosis) (Table 1), that continue to raise the question of a potential etiological association between vascular brain injury and glioblastoma formation.

Criteria for linking brain injuries to brain tumors were proposed over 40 years ago to help clarify their potential causative association, [16] and radiographic modifications have since been suggested [17]. These criteria include: injury severe enough to cause brain contusion and scar formation visible on CT or MR imaging, injury location corresponding to the subsequent radiographic and histological location of the subsequent tumor, a minimum 1-year gap between brain injury and tumor appearance, [16] and a contrast CT or MRI soon after the resolution of the traumatic contusion should not reveal a mass lesion [17]. Our first case fulfills these criteria. Our second case and 50% of the cases identified in the literature review (Table 1) fulfilled all but the temporal latency criterion. However, glioblastoma tumor volume has been reported to double over the course of only fifty days, with faster growth in the smallest tumors (<3.88 mL) [18], raising the question of whether this latency criterion should apply to glioblastoma, particularly in cases in which there is no radiographic evidence of tumor at the time of initial vascular injury (Fig. 2C).

2.2. Central nervous system injury and transformation to the glioblastoma microenvironment

Brain injury results in astrocytic activation [19] with consequent growth factor expression, cellular migration, and proliferative capacity [20,21], features that are shared with glioblastoma development. For example, ischemic injury has been shown to induce astrocytic expression of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-alpha, as well as transcriptional factors known as hypoxia inducible factors (HIFs) which support astrocytic proliferation and have been linked to tumorigenesis [22]. Another inflammatory molecule, connective tissue growth factor (CTGF), suppresses expression of cell-to-cell adhesion molecules, which promotes both inflammatory cell and tumor cell invasion