No Circulating Cytomegalovirus in Five Patients with Glioblastoma Multiforme

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Abstract. *Background: Glioblastoma multiforme is the most common and most aggressive type of primary brain tumor, accounting for 52% of all primary brain tumor cases and 20% of all intracranial tumors. Recently, evidence for a viral cause has been postulated, possibly SV40 or more likely cytomegalovirus (CMV). One report indicated that 80% of patients with newly diagnosed glioblastoma multiforme have detectable cytomegalovirus DNA in their peripheral blood, while sero-positive normal donors and other surgical patients did not exhibit detectable virus. Patients and Methods: In the current study, we examined peripheral blood of 5 patients with newly diagnosed glioblastoma multiforme. Peripheral blood was collected in anticoagulated tubes from five patients with newly diagnosed glioblastoma multiforme referred for radiation therapy. We used standard methods for detecting CMV by reverse transcriptase–polymerase chain reaction (RT-PCR) and peripheral blood culture. Results: None of our patients had circulating CMV. Conclusion: There are four subtypes of glioblastoma. We hypothesize that circulating CMV might be limited to some, but not all of these subtypes, and that our failure to detect CMV might be attributed to the fact that none of these patients had the appropriate subtype or subtypes.*

Glioblastoma multiforme is the most common and most aggressive type of primary brain tumor, accounting for 52% of all primary brain tumor cases and 20% of all intracranial tumors (1). Glioblastoma multiforme is more common in males and appears to be sporadic, without any genetic predisposition. No links have been found between glioblastoma multiforme and smoking, diet, cellular phone use, or electromagnetic fields. The only effective chemotherapy is temodar, an oral alkylating agent, that seems to work as a radiosensitizer (2).

Recently, evidence for a viral cause has been postulated, possibly SV40 (3) or more likely cytomegalovirus (CMV) (4). Cobbs *et al*. reported that a high percentage of malignant gliomas are infected by CMV and multiple CMV gene products are expressed in these tumors (5). Mitchell *et al*. reported that 80% of patients with newly diagnosed glioblastoma multiforme have detectable cytomegalovirus DNA in their peripheral blood, while sero-positive normal donors and other surgical patients did not exhibit detectable virus (4). Mitchell *et al*. suggest an association of CMV with malignant gliomas and propose that subclinical CMV viremia is a previously unrecognized manifestation of glioblastoma multiforme.

In the current study, we examined peripheral blood in five patients with newly diagnosed glioblastoma multiforme.

Patients and Methods

Peripheral blood was collected in anticoagulated tubes from five patients with newly diagnosed glioblastoma multiforme referred for radiation therapy. We used standard methods for detecting CMV by reverse transcriptase–polymerase chain reaction (RT-PCR) (6) and peripheral blood culture (7). Characteristics of the patients are listed in Table I.

Results

None of our five patients had circulating CMV detected either with RT-PCR or blood culture. Mitchell *et al*. reported that 80% of patients with newly diagnosed glioblastoma multiforme have detectable cytomegalovirus DNA in their peripheral blood (4). Therefore, the chance of a single glioblastoma patient not having detectable cytomegalovirus would be 20% or 0.2, and the chance of none of five patients having detectable cytomegalovirus would be $(0.2)^5$ or p=0.00032.

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Table I. *Characteristics of patients in this study. All lesions were primary except for the 22-year-old male, whose tumor arose in the site of an oligodendroglioma treated at age 14.*

Age	Gender	Karnofsky score	Presentation	Size (cm)	Position
47	F	100	headaches	4	r. ant temporal
70	M	60	gait disturbance	5	r. temp
22	M	80	seizure	4	l. temp
69	F	90	cognitive disturbance	5	r. parietal
52	M	60	cognitive disturbance, headaches	6	r. frontal

Discussion

CMV is one of 8 human herpesviruses. CMV infects at least half of the population in developed countries, and nearly everyone in developing countries, where poor sanitation and hygiene abet its transmission. Although it generally does not cause problems in healthy adults, CMV is a common cause of birth defects, and it can cause a host of serious problems in immunocompromised people, particularly AIDS patients, who often develop CMV chorioretinitis (8). Moreover, increased CMV antibody levels are associated with impaired cognition, frailty, functional impairment, and increased mortality among community-dwelling older adults (9).

The CMV–glioblastoma association is controversial. It is unclear why CMV, a common virus, would cause glioblastoma in only a small subset of those infected, especially since *in vitro* studies have failed to show that CMV transforms normal cells into cancerous cells. Yet some preliminary results indicate Valcyte (Roche), an antiviral drug, may improve prognosis in glioblastoma patients, despite the questionable CMV association (8).

Our own inability to find circulating CMV in five glioblastoma multiforme patients might be explained by the recent discovery of four genomic glioblastoma multiforme subtypes (10, 11). We hypothesize that circulating CMV might be limited to some, not all, of these subtypes, and that our failure to detect CMV might be attributed to the fact that none of these five patients had the appropriate subtype or subtypes. A larger study would be worthwhile.

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