Glioblastoma multiforme in a case of acquired immunodeficiency syndrome: investigating a possible oncogenic influence of human immunodeficiency virus on glial cells

Case report and review of the literature

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Malignant glioma is the most common primary brain neoplasm, but generally it is not included in the differential diagnosis of enhancing lesions of the central nervous system (CNS) in patients suffering from acquired immunodeficiency syndrome (HIV). Primary CNS lymphoma was suspected, making a definitive histological diagnosis crucial. An initial stereotactic biopsy sample was insufficient to establish a diagnosis and a second biopsy of the lesion was obtained. The histopathological investigation confirmed GBM and adjuvant external radiation treatment was given to the patient, who survived for 4 months after the initial biopsy. A decline in the rate of Toxoplasma infection and the changing diseases observed in HIV infection indicate the importance of obtaining a biopsy in cases of CNS mass lesions.

KEY WORDS • acquired immunodeficiency syndrome • human immunodeficiency virus • infection • glioma • lymphoma • Toxoplasma

RECENTLY, a shift toward more cases of PCNSL and fewer cases of toxoplasmosis has been documented in the frequency of CNS enhancing lesions found in cases of HIV infection.1 This overall increase in the incidence of the PCNSL in patients with AIDS has been implicated as a contributor to the general increase in PCNSL. Although the incidence of PCNSL is increasing, before the year 2000 it is not expected to surpass glioma as the most frequently diagnosed intracranial malignancy.7 The occurrence of glial cell tumors in patients with AIDS-related focal mass lesions has been reported to be approximately 6% in two small series.19,27 Brain biopsy has not been performed in most large series in which focal mass lesions in patients with HIV have been described because biopsies are considered nondiagnostic.13,27 A presumptive diagnosis of PCNSL in patients with HIV who have focal cerebral mass lesions may be just as erroneous as a presumptive diagnosis of TE followed by empirical antitoxoplasma treatment.21 Therefore, brain biopsy may be indicated in atypical cases. The occurrence of glioma in patients with AIDS appears to be more than coincidental and has implications in the clinical management and etiopathogenesis of tumors in these patients.2,5,19,21

Case Report

History. This 29-year-old man with an established diagnosis of AIDS complained of relentless headaches and was referred to the neurosurgical service. The results of an MR image of the brain obtained 3 years previously for nonspecific complaints were negative for any focal mass lesions. Primary CNS lymphoma was suspected, making a definitive histological diagnosis crucial. An initial stereotactic biopsy sample was insufficient to establish a diagnosis and a second biopsy of the lesion was obtained. The histopathological investigation confirmed GBM and adjuvant external radiation treatment was given to the patient, who survived for 4 months after the initial biopsy. A decline in the rate of Toxoplasma infection and the changing diseases observed in HIV infection indicate the importance of obtaining a biopsy in cases of CNS mass lesions.

Abbreviations used in this paper: AIDS = acquired immunodeficiency syndrome; CNS = central nervous system; CT = computerized tomography; GBM = glioblastoma multiforme; HIV = human immunodeficiency virus; MR = magnetic resonance; PCNSL = primary central nervous system lymphoma; TE = Toxoplasma encephalitis.
formed. Histopathological examination of the specimen revealed an increase in glial cells and focal calcification; no abnormal lymphoid proliferation was observed.

**Medical Management and Second Biopsy.** The patient was started on a steroid regimen. His symptoms worsened and he developed behavioral disturbances and weakness of both upper and lower extremities on the left side. A repeated CT scan revealed increased edema and tumor size. A malignant glioma was suspected and a second stereotactic biopsy was performed. The tissue this time showed features of GBM with pleomorphic astrocytes, vascular proliferation, and areas of necrosis (Fig. 2). Staining for glial fibrillary acidic protein was strongly positive in many tumor cells (Fig. 3).

**Additional Treatment.** The patient’s recovery following the biopsy procedure was uneventful. Treatment and prognosis were discussed in detail with the patient, who agreed to undergo external-beam radiation treatment for local disease control. A total of 60 Gy in 30 fractions was planned. The patient received 12 Gy in six fractions before he succumbed to his disease. He survived for 4 months after the first biopsy and 1 month after the diagnosis was established.

**Discussion**

Neurological involvement in patients with HIV is common. Approximately 40 to 60% of patients with AIDS present with some neurological disorder at some stage of the disease. The most common focal intracerebral pathological entities reported are TE, PCNSL, progressive multifocal leukoencephalopathy, tuberculoma, and cryptococcoma. In 10 publications appearing from 1985 to 1994, we found 19 cases in which patients with AIDS were reported to have gliomas (Table 1). In two reports of four cases each, there was an approximately 6% incidence of gliomas in AIDS patients with cerebral mass lesions. Forty-five percent of these tumors were Grade II differentiated astrocytomas, 23% were anaplastic astrocytomas, and 27% were GBMs. The majority of these patients died within 3 months of diagnosis (86%). Two died of complications of surgery (intracerebral hemorrhage and postoperative pulmonary embolus) and one died of systemic disease. All other deaths were a result of the progressive effects of the brain tumor. Among those patients with GBM, all but two died of tumor progression. All of these patients were male, with a mean age of 34.5 years (stand-
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standard deviation 7.6 years). Age at onset of gliomas in patients with HIV infection is younger than that in the general population, suggesting an influence of HIV on the oncogenicity of glial cells.

Nonlymphomatous brain tumors are not considered to be AIDS-defining diseases in the HIV-positive population, and the occurrence of gliomas is generally considered to be coincidental. However, epidemiological studies have shown that these non–AIDS-defining malignancies are on the rise. Recent literature suggests that there may be strong oncogenic influences of HIV on glial cells. The HIV-1 infection of human glial cells in vitro is well established, and the virus is known to infect cells of neurectodermal origin. The entry of HIV-1 into glial cells is independent of CD4 and may be mediated by an alternative receptor. The relative resistance of glial cells to the virus and the persistence of the virus in the host may initiate a transformation process that could be a key step in the induction and growth of astrocytomas. The HIV-1 can induce the production of interleukin-1, -6, and -8, and tumor necrosis factor–α and alter their expression; this can contribute to immunosuppression and the emergence of neoplasia. Tumor necrosis factor–α is mitogenic to astrocytes, and the finding of astrocytosis as an early and consistent feature in the brains of patients with HIV may be considered a nonspecific inflammatory response against the virus. The astrocytosis that involves cell cycling might be a prerequisite for malignant transformation in tumors and might also increase the risk of malignant transformation in glia. Transforming growth factor–β, a multifunctional cytokine, has a potent immunosuppressive effect and is detected in the CNS of AIDS patients, but is not detected in healthy brains. It is also overexpressed in a majority of astrocytomas and GBMs, but is absent in healthy brains, thus facilitating the escape of neoplastic astrocytes from immune surveillance. The overexpression of transforming growth factor–β in patients with AIDS might allow the emergence of malignant clones from the pool of proliferating astrocytes, and immunosuppression caused by HIV might also encourage the induction of neoplasms. Another possibility is that these tumors may relate to coinfections by viruses that are well known to be oncogenic.

A third possibility is that AIDS patients undergo more frequent brain CT and MR imaging examinations than their age-matched cohorts. There is a low threshold at which patients with HIV and headache or focal deficits are selected for imaging. Furthermore, systemic illness causing fever or electrolyte imbalance may make these patients more prone to seizures, prompting neuroimaging studies. Thus, these tumors may be detected more frequently, before they become necessarily symptomatic and are confirmed by biopsy. Furthermore, the factors mentioned previously may account for premature growth acceleration in lesions predating HIV infection, producing more malignant glial tumors. In light of these observations, it is highly possible that glial tumors arise from complex interactions of many factors and their emergence is facilitated by the immunological abnormalities that occur in patients with AIDS.

The differential diagnosis of mass lesions of the brain in patients with AIDS should include gliomas. Biopsy is recommended by many authors to exclude these lesions.

Selective indications for biopsy may be outlined from judicious application of single-photon emission CT combined with an analysis of cerebrospinal fluid for Epstein–Barr virus DNA. The decision to treat these patients is based on a number of factors, including the patient’s desire to be treated (as in the present case), the expected quality of life, and the expected length of survival.

Establishing the correct diagnosis has significant impact on the length of patient survival. Poor outcome in many of these cases may be related to difficulties encountered in establishing the correct diagnosis. In the majority of these cases, TE was the first consideration and the patients were treated empirically, rather than establishing the diagnosis by biopsy. Although the incidence pattern of CNS lesions in patients with AIDS has changed so that TE is now less common than PCNSL, gliomas are by far the most common primary nonlymphomatous intracranial neoplasm. A routine histopathological diagnosis of focal mass lesions in patients with AIDS might disclose gliomas to be more common than currently recognized. Encouraging results from zidovudine therapy, adjuvant radiotherapy, and chemotherapy demonstrate the importance of making an early correct diagnosis in these patients. The length of time required for an accurate diagnosis is key: an intensive therapeutic approach, if instituted early in the course of the disease, may be successful.

**References**


