Gliomas and brain lymphomas in HIV-1/AIDS patients: reflections from a 20-year follow up in Mexico and Brazil

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Abstract

Opportunistic infections and invasive primary tumors represent major causes of morbidity and mortality in HIV-1-infected individuals. HIV-1 involvement of the central nervous system (CNS) affects nearly half of seropositive patients, being the primary CNS lymphoma (PCNSL) a hallmark neoplasia of this population. Interestingly, the incidence of other brain tumors (e.g. gliomas) is exceedingly rare in AIDS patients, and their co-morbidity has been limited to case reports. Here, we share our 20-year experience following brain tumors in HIV-1/AIDS patients from major referral hospitals in Mexico and Brazil. Additionally, we provide the most updated compilation of reported glioma cases in AIDS patients, with a thorough epidemiological analysis. Furthermore, we discuss HIV-1-driven mechanisms that would theoretically increase malignant transformation of glial cells; while offering newly reported explanations as to why protease inhibitors, key components of multi-drug anti-retroviral schemes, may be responsible for such a low co-incidence of gliomas in HIV-1 infected individuals.

Review

Neurocognitive impairment remains a major burden for HIV-1/AIDS patients. Even when highly active antiretroviral therapy (HAART) has become widely available, neurological manifestations affect up to 50% of seropositive individuals.^{1,2} The spectrum of HIV-1-associated neurological disorders is wide, and encompasses complications that can be either primarily related to the retrovirus itself (e.g. AIDS dementia complex), or secondary to opportunistic infections, malignant neoplasms, or the reconstitution of the immune system.³⁻⁵ Over the last 20 years, as we have followed the AIDS epidemic develop all

over the world, we have noticed clear-cut differences in the incidence, prevalence and clinical presentations of neurological complications reported among industrialized nations to those reported from developing countries.^{2,6,7} Such dramatic differences depend on numerous factors that include: the location of the reporting institution, availability to HAART, diagnostic tools, treatment guidelines, and the endemic microbiological repertoire.^{4,8-11}

As HIV-1 infection progresses, defective immunosurveillance mechanisms favor uncontrolled proliferation of malignant cells. Importantly, Epstein Barr virus, the causative agent of infectious mononucleosis, induces aberrant genotypical changes and malignant transformation on infected B cells within the CNS.¹² Inherent to the immunocompromise experienced in the context of HIV-1 infection, these malignant cells undergo uncontrolled clonal expansion forming extranodal foci of lymphoproliferative cells that may give rise to primary CNS lymphomas (PCNSL). Importantly, this neoplasm is exclusively observed in severely immunocompromised populations, and its presence was found in ~5% of HIV-1 seropositive patients before the introduction of HAART (Figure 1).¹³

Conversely, primary intracranial tumors derived from other cell lineages are rarely developed in HIV-1/AIDS patients, with a total number of 55 reported cases, ever since the epidemic started in the early 1980's.^{2,6,14-36} Gliomas, the most common type of primary brain neoplasm reported in otherwise healthy individuals,³³ arise from malignant transformation of neuroectodermal-derived supporting cells. The pathogenesis of these tumors has been associated with mutations in the p53 tumor suppressor gene,³⁷ or the p16/RB/E2F pathway.³⁸ While the annual incidence of gliomas in the general population is reported to be around 3.85 cases per 100,000 individuals,³⁹ malignant gliomas, including glioblastoma multiforme (the most common type of glioma), do not appear to be in the list of differential diagnoses of an occupying brain lesion in HIV-1/AIDS patients.

Such a rare coincidence obliged us to perform a systematic retrospective review and careful analyses of the reported brain gliomas in HIV-1 seropositive individuals, comparing populations from industrialized nations with two Latin American countries with universal access to HAART, Mexico and Brazil.

In addition, we discuss relevant evidence that would theoretically support an enhanced incidence of gliomas in HIV-1/AIDS patients, while offering alternative perspectives based on recent publications, which may offer insights into the factors promoting a protective activity for the development of gliomas in seropositive patients under HAART.

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NeuroAIDS in Mexico, a retrospective view of primary central nervous system lymphoma and glioma cases reported in major referral health institutions

A few years after the first AIDS cases were reported in the early 1980s, HIV-1 spread south of the US border. Infectious-disease specialists experienced major challenges, as the array of clinical manifestations exhibited by HIV-1/AIDS patients in Latin America differed from those observed in US-based health institutions. Importantly, we performed one of the first studies depicting such discrepancies.² In that report, a broad comparison of HIV-1-related neurological manifestations among American and Mexican seropositive patients was depicted in a cross-sectional and retrospective study that included 500 cases from Houston, Texas, and 120 cases from a cohort in Mexico City. Clinical reports, laboratory and imaging data of HIV-1 patients experiencing neurological manifestations concluded that the prevalence of PCNSL was dramatically higher in the US population than it was in Mexico (8.4% vs. 2.5%), while opportunistic infections such as intracranial tuberculomas were observed exclusively in the Mexican cohort.² Of note, no gliomas were found in the Mexican population, while 2 cases of gliomas were reported in the American cohort² (Figures 2-3).

Years later, another retrospective analysis of AIDS patients evaluated at the National Institute of Neurological Diseases in Mexico City during a 9-year time frame (1990-1998), found a PCNSL prevalence of 1.3% (Figure 1), with an identical prevalence for gliomas (1.3%, 2/149).³⁴ Notably, a case of glioblastoma multiforme and an oligodendroglioma were reported in this Mexican study (Figure 4). More recently, a large retrospective study suggested a significant reduction in the prevalence of PCNSL

(0.3%) (Figure 1), an effect attributed indirectly to the widespread use of HAART.⁴¹ Since 1998, no more glioma cases have ever been reported in AIDS patients from any health center in Mexico (Figure 2). Similarly, we have also followed up AIDS cases for 15 years in a major referral institution located in Monterrey, the third largest city in the Mexico. Collectively, in over 20 years of AIDS epidemic only 2 cases of gliomas have ever been reported in Mexico (Figures 2-3). This picture is similar to other developing nations in Africa and Asia where the number of reported cases does not parallel their close surveillance and thorough experience in neuroAIDS (Figure 3).

Brazil, a different country with a similar story

According to the United Nations Programme on HIV/AIDS, Brazil has between 600,000 and 890,000 people living with AIDS.⁴¹ Importantly, this Latin American Country has free and universal access to HAART, situation that allows measuring the impact of AIDS treatment in the prevalence of neurological manifestations, including primary tumors. During the past 15 years, over 50,000 patients have been admitted to the infectious-disease service of Instituto Emilio Ribas in Sao Paulo. A high number of patients undergo extensive laboratory and imaging workups for suspected intracranial masses, being CNS toxoplasmosis, cryptococcosis and progressive multifocal leukoencephalopathy the most common diagnoses. Moreover, other comprehensive studies performed in Rio de Janeiro have reported frequencies of PCNSL of ~4%.⁴² In over 20 years of AIDS epidemic in Brazil, just a single case of glioma has been reported in HIV-1 seropositive individuals³⁵ (Figure 2), reproducing a phenomenon observed throughout most of the developing world (Figure 3).

Gliomas and HIV-1, is highly active antiretroviral therapy responsible for their low co-incidence?

While HIV-1-driven defective immunosurveillance generally favors tumor growth and metastasis, cumulative evidence of over 20 years following the AIDS epidemic demonstrates that HIV-1-infected individuals rarely develop gliomas.⁴³ Nevertheless, HIV-1 tropism and infectivity in the brain is not limited to microglia/macrophages, but has been shown to also include astrocytes, which represent a potential reservoir for further productive infection.^{44,45} In fact, astrocytes have been reported to be preferentially infected by virulent HIV-1 T-tropic strains through different interactions via the V3 loop,⁴⁶ and undergo enhanced malignant proliferation *in vitro* via Nef-mediated mechanisms.⁴⁷ Furthermore, HIV-1-driven

cytokines like TNF- α , and TGF- β may promote oligodendrocytic differentiation and proliferation, theoretically favoring tumor development.^{43,48} However, recent evidence unveiled a direct mechanism responsible for controlling glioma growth in HIV-1/AIDS patients.^{49,50} These independent studies depict two ways by which protease inhibitors; medications commonly used in combination therapy with reverse transcriptase inhibitors to dampen HIV-1 infectivity, can abrogate glioma growth. First, Pyrko P, *et al.*, described how Nelfinavir and Atazanavir induce apoptosis in

gliomas by triggering endoplasmic reticulum stress.⁴⁹ Concomitantly, Pore N, *et al.*, described how Nelfinavir and Amprenavir decreased vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF)-1 α expression, leading to impaired angiogenesis in glioblastoma multiforme tumors injected into nude mice.⁵⁰ Nonetheless, while these experimental data reproduces *in vivo* effects seen in HIV-1/AIDS patients under HAART, further detailed mechanisms by which protease inhibitors might prevent glioma development remain to be elucidated.

Figure 1. HAART has reduced the number of PCNSL cases in AIDS patients. Graphical representation of the prevalence of PCNSL in patients with HIV-1/AIDS during 3 decades. References are indicated within brackets.

Figure 2. Reports of gliomas in HIV-1/AIDS patients follow a Gaussian distribution during the first three decades of the epidemic. Graphical representation of the total number of gliomas reported in Mexico/Brazil and the rest of the world, classified per decade. References are indicated within brackets.

Figure 3. Gliomas in HIV-1/AIDS patients are more commonly reported in Western Industrialized World. Graphical representation of the cumulative cases of gliomas reported in AIDS patients and their distribution per continent. References are indicated within brackets.

Figure 4. Glioblastoma multiforme is the most common type of reported glioma in HIV-1 seropositive individuals. Graphical representation of the distribution of gliomas reported in AIDS patients by histological type. References are indicated within brackets.

Discussion

While primary CNS lymphomas have been a major cause of morbidity in HIV-1/AIDS patients; the incidence of gliomas, the most prevalent brain tumor in seronegative populations, has always been negligible. With a cumulative number of 55 reported gliomas in AIDS patients ever since the beginning of the epidemic, we hypothesize that there may be a protective role of HIV-1 that restrains glioma growth (Figures 2-4). Importantly, we have noticed an important trend; glioma cases were specially reported from Western European Countries and the US during the period comprising the years 1991-2000, where most people still did not have full access to HAART (Figure 4). Interestingly, between the years 2001 and 2010, where HAART became widely available, only 5 out of 55 total glioma cases were reported (Figure 2). Furthermore, our analysis of the reported gliomas according to their histological classification (Figure 4) reveals that glioblastoma multiforme is the most prevalent type of glioma seen in HIV-1/AIDS patients (19/55), similar to what has been reported for HIV-1 seronegative populations. In fact, all other types of gliomas, which commonly affect seronegative patients, including low grade astrocytomas and anaplastic astrocytomas are minimally represented.

In conclusion, although there is compelling evidence showing a direct role of protease inhibitors as mediators of apoptosis and inhibitors of angiogenesis in gliomas, further epidemiological and basic science research needs to be performed in controlled conditions in order to elucidate if there are other factors responsible for the protective anti-glioma effect seen in HIV-1/AIDS patients.

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