

AIDS related malignancies in Brazil

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Purpose of review

There have been relatively few studies of HIV-related malignancies in Brazil. Universal access to antiretroviral drugs in Brazil has changed both the mortality and morbidity rates of AIDS. Nevertheless, there is also extreme poverty in both urban and rural areas and complications of prolonged immune suppression such as mycobacterial and malignant diseases have put a significant strain on the country's healthcare system. This brief review outlines the existing data regarding AIDS related malignancies in the largest Latin American country.

Recent findings

Currently, there are almost 600 000 people infected with HIV in Brazil and 170 000 patients are receiving highly active antiretroviral therapy. In the studies done of HIV malignancies in Brazil, it appears that these tumors are histologically similar to those that occur in other equatorial countries and differ somewhat from those seen in Europe and the US. Another unique distinction is the high association with oncogenic herpes viruses.

Summary

The existence of federally sponsored highly active antiretroviral therapy, clinicians and healthcare providers experienced in the care of HIV patients and high incidence of malignancies associated with oncogenic viruses make Brazil an important site for clinical and basic research in AIDS and immunodeficiency related malignancies.

Keywords

Brazil, HAART, HIV, HTLV-I, Kaposi's sarcoma, lymphoma

Abbreviations

ARL	AIDS related lymphoma
EBV	Epstein–Barr virus
HAART	highly active antiretroviral therapy
HHV	human herpes virus
HPV	human papillomavirus
HTLV-I	human T cell leukemia virus type I

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Introduction

Brazil has the highest number of cases of AIDS in Latin America. From 1980 to June 2006, a total of 433 000 cases were reported. Since the introduction of the government mandated program to provide highly active antiretroviral therapy (HAART) in 1996, the survival of patients has markedly improved [1]. Although this has resulted in a dramatic decrease in the number of cases of AIDS (versus those predicted prior to the institution of the program) there is still extreme poverty in both urban and rural areas and complications of HIV related diseases such as malignancies have put a significant strain on an overburdened healthcare system. There have been a limited number of studies of HIV related malignancies in Brazil. These tumors appear to be histologically similar to those that occur in other equatorial countries and differ somewhat from those seen in Europe and the US. One distinction is the high association of Brazilian AIDS related lymphomas with oncogenic herpes viruses, particularly Epstein–Barr virus (EBV) [2,3]. Other unique aspects of the HIV epidemic in Brazil such as the high incidence of dual infection [HIV and human T cell leukemia virus type I (HTLV-I)] remain relatively understudied. We summarize here some of the current data regarding AIDS related malignancies in the largest Latin American country.

Non-Hodgkin lymphoma

In the limited number of studies published to date, it appears that AIDS related lymphomas (ARLs) diagnosed in developing countries such as Kenya and Brazil are more highly associated with EBV [2,4,5]. This is not limited to ARL. The marked association between Burkitt type lymphomas seen in equatorial Africa and EBV has also been reported in some regions of Brazil. Araujo *et al.* [6] reported an 87% association with EBV among 54 cases of Burkitt lymphomas from the northeastern state of Bahia. Among these, the lytic protein BZLF-1 was

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detected in 8% by immunohistochemistry and nearly all expressed a type I latency pattern. In another study, Sandlund *et al.* [7] reported 98 cases of pediatric Burkitt lymphoma from Recife, another northeastern Brazilian city. There was a striking predominance of abdominal presentation (versus mandibular presentation commonly seen in Africa) and most were EBV+ (93%). In the largest published study to date on viral co-infection in ARLs from various regions in Brazil, 55% of cases (11 of 20) were positive for EBV, as determined by EBV-encoded RNA staining. As has been reported in other series the majority of these cases were large cell or immunoblastic lymphomas [2]. In general Burkitt lymphomas from the northeast appear to be more tightly linked to EBV. Similarly, HIV related lymphomas from this region are also more likely to be associated with EBV. A recent study of 17 ARLs in Bahia revealed that 71% were associated with EBV [3]. Two studies from investigators in São Paulo, one a retrospective analysis of 78 patients with ARL and another, a study of the significance of p-glycoprotein (MDR-1) on clinical outcome were recently published [8,9]. A previous diagnosis of an AIDS defining illness inversely correlated with complete remission and both response and survival were adversely affected by p-glycoprotein expression that was detected in 27 of 45 (60%) of samples from patients without previous cytotoxic therapy.

Kaposi's sarcoma

There have been many limited studies and case reports of Kaposi's sarcoma from Brazil. Most have originated from epicenters of HIV infection in the country and the risk groups for Kaposi's sarcoma in Brazil reflect those found elsewhere. As expected, these tumors are all associated with human herpes virus (HHV) type 8 [10]. In a large study of 107 Kaposi's sarcoma patients diagnosed from 1995 to 1998, the majority were men (94%) with a median age of 37 years. In 25% of these cases, Kaposi's sarcoma was the AIDS defining disease [11]. The overall seroprevalence of HHV-8 in gay men in Brazil is similar to a matched population in the US [12]. Several recent reports have focused on serologic studies of HHV-8 in various Latin American populations [13,14]. As would be expected given the variable results of HHV-8 serology reported elsewhere, seroprevalence rates as well as methodologies have differed substantially. In an interesting study of Brazilian Amerindians in which investigators employed an immunofluorescence assay against HHV-8 latency associated nuclear antigen, a remarkable overall HHV-8 seroprevalence of 53% among 781 individuals was reported [15]. A nested PCR and sequencing study of the K1 open reading frame revealed a variety of molecular subtypes of HHV-8 among 33 patients studied. In a more recent study of 982 Amerindians in which an immunofluorescence assay was employed, a seroprevalence of 56.8% was detected [16]. Kaposi's sarcoma has not been reported in these populations although investigators have

hypothesized that this may be due to oral rather than sexual transmission of HHV-8 and the overall lack of HIV infection.

Although no published data are available on the effect of widely available HAART on the incidence of AIDS related Kaposi's sarcoma in Brazil, it is likely to have had a profound effect as has been noted in the US. The availability of both effective antiretrovirals as well as modern chemotherapy such as liposomal anthracyclines make Brazil an ideal site to perform clinical/translational trials for Kaposi's sarcoma and these will soon be undertaken by the US National Cancer Institute sponsored AIDS Malignancy Consortium (AMC).

Human papillomavirus-associated neoplasia

Several studies have demonstrated an increased number of human papillomavirus (HPV) genotypes in HIV infected women. In the largest study to date (208 HIV infected women), a high prevalence of multiple genotypes (78.9%) was observed. HPV-6 was the most common genotype (39.2%), followed by types 51 (31.9%), 11 (26.0%), 18 (24.0%), and 16 (22.5%) [17]. The percentage of high-risk genotypes increased with the cytological classification although there were no significant associations between the number of HPV genotypes detected, cytological classification, HIV viral load, and CD4 count. Surprisingly although there are reports of HPV associated anogenital neoplasia in HIV infected Brazilian women there are none in the medical literature of this disease in men.

Co-infection with other oncogenic viruses

Co-infection with HIV and HTLV-I is an interesting phenomenon of the AIDS epidemic and is spreading to areas where the oncogenic retrovirus is endemic [18–20]. Although there does not appear to be a unique form of malignancy attributed to dual infection, there is evidence that alteration in common markers used to follow HIV disease, specifically CD4+ lymphocyte counts, may be elevated despite severe immune deficiency [19,20]. This has been reported in patients from regions of Brazil that have particularly high seroprevalence rates of HTLV-I [19]. Initial studies by our group have indicated that this is generally a polyclonal rather than clonal T cell expansion, presumably driven by the HTLV-I virus. Whether dual infection hastens the development of HIV related immunosuppression or T cell lymphoma has not been definitively determined. This has substantial clinical relevance in regions where both retroviruses are found since CD4 counts may be an inadequate surrogate marker of immunocompetence in these patients.

In a large retrospective study of 833 AIDS patients, 33% were reportedly seropositive for hepatitis C virus [21].

These patients had a higher mortality although this was thought to be multifactorial. This study was hepatitis C in patients in the pre-HAART era. A more recent study demonstrated a seroprevalence of hepatitis C virus of 42% among 592 anonymously tested HIV-positive participants [22*].

Conclusion

AIDS related malignancies are quite common in Brazil although clearly underreported. Most of the surveillance efforts have justifiably been devoted to the HIV epidemic itself. This is also generally the case in other developing countries. Although some diseases such as endemic and HIV related Kaposi's sarcoma have received substantial attention in sub-Saharan Africa others such as ARLs have not. There are efforts underway to further clinical and basic research in AIDS related malignancies in Brazil. As part of an initiative funded by the AMC and other US National Institutes of Health sources, we are concentrating on identifying patients with these diseases and initiating clinical trials. Through these efforts and improved surveillance, we have recently documented a marked increase in the number of reported cases of ARL. Studies on the molecular biology and pathology of these tumors utilizing newer approaches such as tissue-microarrays are underway. Brazil, in many ways, offers a unique opportunity for clinical and basic research on these tumors. The challenge of providing antiretroviral therapy to study participants largely does not exist. The spectrum of malignancies is reminiscent of both those seen in Africa as well as developed western nations. There are also outstanding investigators and well equipped universities and government institutions to perform the clinical and basic research studies necessary to fully characterize ARL in Brazil.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 532).

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