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AIDS and associated malignancies

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ABSTRACT

AIDS associated malignancies (ARL) is a major complication associated with AIDS patients upon immunosuppression. Chronically immunocompromised patients have a markedly increased risk of developing lymphoproliferative disease. In the era of potent antiretrovirals therapy (ARV), the malignant complications due to HIV-1 infection have decreased in developed nations where ARV is administered, but still poses a major problem in developing countries where HIV-1 incidence is high and ARV is still not yet widely available. Even in ARV treated individuals there is a concern that the prolonged survival of many HIV-1 carriers is likely to eventually result in an increased number of malignancies diagnosed. Malignancies that were found to have high incidence in HIV-infected individuals are Kaposi's sarcoma (KS), Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). The incidence of NHL has increased nearly 200 fold in HIV-positive patients, and accounts for a greater percentage of AIDS defining illness in the US and Europe since the advent of HAART therapy. These AIDS related lymphomas are distinct from their counterparts seen in HIV-1 seronegative patients. For example nearly half of all cases of ARL are associated with the presence of a gamma herpesvirus, Epstein Barr virus (EBV) or human herpesvirus-8 (HHV-8)/ Kaposi's sarcoma associated herpesvirus (KSHV). The pathogenesis of ARLs is complex. B-cell proliferation driven by chronic antigenemia resulting in the induction of polyclonal and ultimately monoclonal lymphoproliferation may occur in the setting of severe immunosuppression.

Keywords: Kaposi's sarcoma, lymphomas, Epstein-Barr virus, KS-associated herpesvirus, human herpesvirus 8.

INTRODUCTION

It has been over twenty years since the onset of the AIDS epidemic, and in spite of the tremendous progress made towards the understanding of the disease, the virus that causes the disease and the development of highly effective anti-retroviral treatments, the number of people infected by HIV is still staggering. As of the end of 2004, it was estimated that there were 39.4 million people newly infected with HIV, and 3.1 million deaths globally (www.UNAIDS.org). Over 2/3 of infections occur in the developing world and sub-Saharan Africa. Concurrent with immunosuppression in the infected individuals are opportunistic infections and AIDS-associated diseases, including malignancies, which have increased substantially during the AIDS disease course [1, 2]. Malignancies that were found to have high incidence of HIV-infected individuals are Kaposi's sarcoma (KS), Hodgkin's disease (HD), non-Hodgkin's lymphoma (NHL), squamous cell carcinomas, plasmacytomas, and leiomyosarcoma in children. These tumors arose due to the lack of appropriate immune response or the reactivation of etiological agents associate with these tumors in immunosuppressed HIV infected individuals. Serveral AIDS-associated malignancies were found to be associated with the viral infections. Among them, Epstein-Barr virus (EBV) was found to associate with NHL, HD, and leiomyosarcoma; Kaposi's sarcoma associated herpesvirus (KSHV) or human herpesvirus-8 (HHV-8) was found to associate with KS and primary effusion lymphoma (PEL), and human papilloma virus (HPV) was found to associate with squamous cell neoplasia. The most common malignancies seen in HIV-infected individuals are KS and HNL, and both have been classified as AIDS-defining illnesses.

AIDS RELATED LYMPHOMAS

The infectious and malignant complications of HIV have

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decreased in developed nations where potent antiretrovirals (ARV) are widely available. However, the prolonged survival of many HIV carriers is likely to eventually result in an increased number of malignancies diagnosed in these individuals. Chronically immunocompromised patients have a markedly increased risk of developing lymphoproliferative disease. The incidence of non-Hodgkin's lymphomas (NHL) is increased nearly 200 fold in HIV-positive patients and accounts for a greater percentage of AIDS defining illness in the US since the advent of HAART therapy [3, 4]. AIDS related lymphomas (ARLs) are distinct from their counterparts seen in HIV seronegative patients. For example nearly half of all cases of ARL are associated with the presence of a gamma herpesvirus, EBV or HHV-8 [5]. ARLs are often diagnosed at a very advanced stage and frequently involve uncommon sites (oral cavity, GI tract, central nervous system) [5, 6]. The pathogenesis of ARLs is complex. B-cell proliferation driven by chronic antigenemia results in the induction of polyclonal, and ultimately monoclonal lymphoproliferation. In addition dysregulation of cytokine pathways (interleukin-6 and interleukin-10), coupled with bcl-6, p53, and c-myc mutations have been implicated in the pathogenesis of ARL [7].

SUBTYPES OF AIDS NHLS

AIDS NHLs may be broadly categorized into several subtypes. Large cell immunoblastic lymphoma (IBL) and diffuse large cell lymphoma (DLCL) generally occur in the setting of moderate to severe immunosuppression (CD4+ lymphocyte counts below 100 mm^3/ml). IBLs and to a lesser degree DLCLs are often associated with EBV. These tumors express the EBV encoded oncoprotein latent membrane protein-1 (LMP-1) [5-7]. LMP-1 may function in a similar manner to tumor necrosis factor receptors by activating cellular anti-apoptotic factors such as Nuclear Factor Kappa B [6, 7]. DLCLs are frequently found to contain genetic alterations in Bcl-6 [8] although the consequences of these mutations have not been fully defined.

AIDS related Burkitt's lymphoma (BL) generally occurs in more immunocompetent patients [9]. AIDS BLs share features with endemic African BL in that both overexpress c-myc due to reciprocal translocations that bring the transactivator under the influence of potent promoter sequences within the immunoglobulin (Ig) genes loci. Inactivating mutations and deletions of p53 are also common as in all types of BL [10]. A distinguishing feature between AIDS related and endemic BL is that the former is associated with EBV far less frequently than the latter [9, 10]. These tumors are incredibly aggressive with brief doubling times. Flow cytometric analysis typically reveals that over 90% are in S phase. Ongoing tumor lysis syndrome even in the absence of concomitant chemotherapy is often noted. AIDS related BLs appear to carry a poor prognosis even when compared to AIDS related DLCL [11].

A recently described variant of ARL, plasmablastic lymphoma, occurs in a small percent of HIV+ patients. These tumors are generally associated with EBV and HHV-8 (10). Response to conventional chemotherapy is poor and some investigators have suggested that viral targeted approaches may be beneficial [12].

A rapidly fatal subtype of AIDS NHL is Primary Central Nervous System Lymphoma (PCNSL). These tumors are most frequently classified as IBLs and occur in the most immunosuppressed patients. In contrast to PCNSL in HIV negative patients they are virtually always associated with EBV [13]. Detection of EBV sequences in the CSF by polymerase chain reaction (PCR) coupled with positive Thallium spectroscopy has proven to be a helpful diagnostic tool [14]. These patients are often afflicted by many complications of HIV infection. Standard therapy with conventional chemotherapy combined with radiation therapy results in only about a 4 month survival although long term remission has been reported in patients treated with high dose Zidovudine and Ganciclovir [15, 16].

The most commonly identified virus associated with AIDS related lymphomas is EBV and there is a large body of published work on the oncogenic mechanisms of this agent [17, 18]. B-lymphocytes transformed by EBV (lymphoblastoid cell lines) in vitro express an array of virus-encoded proteins including six EBV nuclear antigens (EBNAs) and three LMPs. EBNAs are generated from differential splicing of a transcript that arises from one of two promoters (Cp or Wp) [18]. This form of latency is termed Latency III. This form of latency is common in immunoblastic lymphomas [17]. A Type II form of latency where EBNA 1, LMP-1 and LMP-2a are expressed has been identified in some EBV associated lymphomas. In Latency I (typical of Burkitt lymphomas) only EBNA-1 (generated from the Qp promoter) and EBERs are expressed [17, 18]. Recent studies have indicated that some heterogeneity in EBV gene expression and EBNA promoter usage exists among endemic BL [19].

THERAPY OF AIDS NHL

Treatment of the AIDS NHL remains disappointing. Polychemotherapy regimens have produced similar results although regimens that combine potent antiretrovirals with conventional chemotherapy may prove superior [20]. HIV positive patients often have poor bone marrow reserve which compromises the ability to deliver full dose chemotherapy. Concomitant opportunistic infections may also lead to a

decrease in chemotherapy delivery. In general, response and survival rates for common NHL regimens are lower than for an HIV negative population. Complete responses occur but tend to be of shorter duration with frequent relapses. Our experience has been that patients concomitantly diagnosed with HIV infection and lymphomas do better with antiretroviral and anti-lymphoma therapy than do those who develop lymphoma after becoming refractory to antiretrovirals. A recently completed study performed by the NCI sponsored AIDS malignancy consortium (AMC) demonstrated the feasibility of concomitant chemotherapy with HAART [21]. Probably the best reported results for chemotherapy in AIDS NHL were from Dr. Little's group at the National Cancer Institute. Using the EPOCH regimen, the group achieved remission in 22 of 24 patients with a progression free survival of 23 months. These patients had favorable prognostic factors (median CD4+ lymphocyte count of 233 mm^3/ml) [20]. Enhanced toxicity of rituximab and CHOP chemotherapy was recently noted in a large multi-center trial conducted by the AMC [22]. The addition of rituximab to standard-dose CHOP as compared to CHOP alone led to increased infectious complications and deaths attributable to sepsis. It is possible that delayed recovery of humoral immunity could contribute to this increased risk of life-threatening bacterial infections in HIV-infected patients. There have been several reports on the feasibility and efficacy of high dose chemotherapy and autologous stem cell transplant for ARL [23, 24]. It is reasonable to assume that patients with well controlled HIV and good performance status should be considered candidates for this therapy. Newer approaches that may benefit patients with ARL include EBV specific cytotoxic T cells and agents that activate the lytic program of gamma herpesviruses thereby sensitizing the tumors to antivirals [25, 26].

KAPOSI's SARCOMA

Kaposi's sarcoma was first described by Moritz Kaposi in 1872 in several cases of multi-focal pigmented sarcoma in elderly Mediterranean men . There are four forms of KS. The first is known as the classic KS or sporadic KS. They are mainly found in the elderly male population in Mediterranean countries, such as Italy [28]. The lesions tend to be found in the lower extremities and are generally non-aggressive. The second type is known as the endemic-African KS; it is more aggressive than the classic KS and can also involve the lymph nodes. This form of KS was seen in the African continent prior to the HIV epidemic and was found in adults (both male and female) and in children [29]. The third is the iatrogenic form of KS, which normally occurs after transplantation in patients treated with immunosuppressive medication. This form of KS seems to vary in geographical prevalence, and is more common in individuals of Mediterranean descent [30]. The fourth form of KS is the AIDS-KS. This is a very aggressive type of KS, first described in early 1980's in homosexual men [31]. AIDS-KS not only involves skin, but also the lymph nodes and often disseminates to lungs, gastrointestinal track, liver, and spleen.

KS is composed of a mixture of irregular shaped, round capillaries, and slit-like endothelium-lined vascular spaces and spindle-shape cells with infiltrating mononuclear cells. It is not clear whether KS represents a clonal neoplastic process or a polyclonal inflammatory lesion. Studies have shown that varying monclonality, oligoclonality, and polyclonality from lesions of various patients [32]. The origin of the KS spindle cells is also not clear; it has been suggested that KS cells represent a heterogeneous population of cells, arising from a pluripotent mesenchmal precursor cells, and may be of lymphatic endothelial cell origin [33].

HUMAN HERPESVIRUS AND KS

An infectious agent has long been suspected in the development of KS; herpesvirus-like particles were found in short-term KS tissue culture, and were subsequently identified as cytomegalovirus [34], but the involvement of CMV in KS has not been confirmed. In 1994, a novel human herpesvirus was identified by Chang and Moore [35] using representational difference analyses. This virus is now known as KSHV or HHV-8, it is found to be necessary but not sufficient for the development of all types of KS. It is clear that other co-factors, such as immunosuppression, are required for KS development. KSHV is found in all KS lesions, and is mainly located in the vascular endothelial cells and perivascular spindle-shaped cells [36]. KSHV infection is not commonly found in low-risk population but found commonly in individuals at risk for KS.

KSHV belongs to the γ-herpesvirus family, which can further be divided into two subgroups, γ-1 or lymphocrytovirus and γ-2 or rhadinovirus. EBV is the prototype of γ-1 virus and the simian herpesvirus saimini is the prototype of γ-2 herpesvirus [37]. KSHV is classified as a γ-2 rhadinovirus and is the first human virus of this subfamily identified. Like other herpesviruses, HHV-8 is a double-stranded deoxyribonucleic acid (DNA) virus. Its genome is linear, is about 165 kbp in length, and contains at least 87 viral genes. A feature of some DNA viruses, particularly of herpesviruses and KSHV, is the ability of these viruses to incorporate or pirate host genes into their genome: these genes can then play a role in the replication, survival, and transformation functions of the virus. KSHV was found to encode human homologue genes that regulate cell cycling like cyclin D, growth factors like

interleukin 6, or genes that may prevent programmed cell death such as bcl-2. Deciphering the functions of these viral genes will lead to a better understanding of viral pathogenesis and oncogenesis.

Unlike most other herpesviruses, KSHV infection does not seem to be widely distributed in most populations. The detection of KSHV infection relies on the presence of antibodies against either lytic and/or latent antigens and varies among the different tests that were used in different seroprevalence studies. In general, the frequency of infection appears to be low in North America, certain Asian countries, and in Northern European nations such as the United Kingdom and Germany, with most studies reporting a seroprevalence rate in normal blood donors of less than 5% [2, 38-40]. In these countries the seroprevalence of KSHV in different risk groups mirrors the incidence of AIDS KS, with a seroprevalence rate of between 25-50% among homosexual men. In other countries such as Italy, Greece, and Israel, especially Southern Italy, the infection rate seems to be much higher in the general population, and is more variable, ranging between 5-35%. In contrast to North America and Europe, KSHV infection is widespread in the African continent. High seroprevalence rates between 40 to 50 % have been found in Central, West, as well as South Africa [41-44]. Therefore, KSHV seroprevalence tracks very closely with KS, with the highest infection rate in geographic areas where classic or endemic forms of KS are more common. KS has a particularly high incidence in Central African countries like the Republic of Congo, Uganda, and Zambia; these countries also have the highest KSHV infection rates in the world [42]. Very little is known about KSHV infection in China even though EBV infection was found to be ubiquitous. There were only two reported studies in China; the study by Dilnur *et al* [45] found that KSHV was associated with KS in China. The study by Du *et al* [46] in the outskirt of China in the Xinjiang autonomy region, where there is a high incidence of HIV-1 infection, showed that there was a high HHV-8 infection rate. The study found KSHV infection varied among individuals of different racial origin, it was highest in the Khalkhas population at about 48% and lowest in the Kazak and Han population at over 12%, but the specimens were screened without dilution and the reproducibility of the assay was not determined, and the prevalence among different risk groups was not studied. Thus, there is a need to perform a systematic comparison of risk groups using established assays.

PRIMARY EFFUSION LYMPHOMAS

In addition to KS, KSHV has also been associated with several other AIDS-associated neoplasms, primary effusion lymphomas, and multi-centric Castleman's disease. Primary effusion lymphoma (PEL) was first identified as a subset of body-cavity-based lymphomas, which subsequently was called PELs [47]. PELs are unique as they were found to contain KSHV DNA are most frequently found in men and in AIDS patient. This type of lymphoma is distinguished from others as having a distinctive morphology, bridging large cell immunoblastic lymphoma and anaplastic large cell lymphoma. PELs often present as lymphomatous effusions in the pleural, peritoneal, and /or pericardial cavity. These cells usually CD20 negative but often express CD45 marker but lack B-cell-associated antigens. PELs are B cell origin with clonal immunoglobulin gene rearrangements. Most PELs are co-infected with EBV and lack e-myc gene rearrangements. PELs are extremely rare tumors, and estimated to be about 0.13% of all AIDS-related malignancies in AIDS patients in the US [48]. Thus, KSHV-associated lymphomas represent a rare, distinct pathobiologic category which often, but not always, associates with an effusion in AIDS patients. The role of KSHV in the development of these lymphomas is not clear since this type of malignancies is still rare even in the populations with high KSHV seroprevalence rate. However, KSHV has always been found in these lymphomas, suggesting that this virus is necessary, but other factors must be needed for the development of PELs. These factors could be EBV infection and/or immunosuppression. Recently solid tumor variants with plasmablastic features have been reported and these tumors tend to be rapidly fatal although recent data suggests that some PEL lines are quite sensitive to inhibition of NF-κB [49].

MULTI-CENTRIC CASTLEMAN'S DISEASE

Multi-centric Castleman's disease (MCD) has also been associated with KSHV infection. MCD is a rare and poorly understood B cell lymphoproliferative disorder with vascular proliferation in the germinal centers, and is though to be related to immune dysregulation [50]. KSHV is found in almost all cases of MCD in AIDS patients and in about 50 % of cases of MCD in HIV negative individuals, suggesting that there is an association between KSHV and MCD at least in HIV-positive cases [51]. However, the role of KSHV in the pathobiology of MCD is not well understood, and it is not clear whether there are any clinical differences between those with and without KSHV.

IMPACT OF HAART ON KS

Since the beginning of the AIDS epidemic in the early 1980's, AIDS-KS has become one of the most common AIDS-associated malignancies with HIV-infected homosexual males at the highest risk, and those with AIDS had a 50% lifetime rate of developing KS early in the HIV epidemic [52]. However, the rate of AIDS-KS has since

steadily declined both in the US and Europe [53]. It has been suggested that the disease may have shifted from an early disease to a late manifestation during the HIV disease course. Since the introduction of highly active antiretroviral therapy, a further major decrease in AIDS-KS was further observed [54], and therapy has now made AIDS-KS a relatively rare tumor in treated HIV-infected individuals [55]. Several studies have shown that there was a marked decrease in KS incidence since HAART was introduced, a decline of as high as 80-fold was observed. In addition regression of KS following treatment has been reported [4, 56-59]. Interestingly, the reduced KS risk was only observed with HAART, but not with double or single anti-HIV drugs [60]. Even though the incidence of KS in the treated HIV-infected individuals in the western world has decreased dramatically, in the setting where HAART is still not widely available, such as sub-Saharan Africa, AIDS-KS still remains a major problem.

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