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HIV/AIDS-Associated Viral Oncogenesis

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Overview

According to the WHO, there are currently over 36 million people living with HIV globally, but with the successes of the antiretroviral therapy (ART), deaths due to AIDS have continued to decline, and people living with HIV (PLWH) are now living a longer and normal life span. However, non-AIDS-associated diseases are now increasing in PLWH, and cancer has now become a leading cause of morbidity and mortality. It has been estimated that cancer is responsible for over one-third of all deaths in HIV-infected individuals. The majority of cancers in AIDS patients are known to associate with co-infection with known oncogenic viruses such as human papilloma virus (HPV), Epstein Barr virus (EBV), the Kaposi's sarcoma associated herpesvirus (KSHV) or human herpesvirus-8 (HHV-8), as well as hepatitis B (HBV) and hepatitis (HCV), and more recently the Merkel cell polyoma virus (MCPyV). With the successes of ART, a number of the AIDS-associated malignancies such as Kaposi's sarcoma (KS) and some lymphomas have declined in the developed countries, but the KS disease burden remains high in Africa; the incidence of KS has reported to be as high as prostate cancer in the US. In addition, several additional non-AIDS defining malignancies (NADM) like anal cancers, oropharyngeal cancers, Hodgkin lymphomas, hepatocarcinomas, and even lung cancers are occurring more often in PLWH. Therefore, there is still an urgent need to have a better understanding of the epidemiology of these cancers, the risk factors involved, the clinical presentations, the treatment, and their associate viral etiological agents, including the viral gene functions, and their effects on the host in leading to cellular transformation and oncogenesis.

This book *HIV/AIDS-Associated Viral Oncogenesis* edited by Meyers represents a must read material for clinicians, researchers, and students who are interested in this area. It consists of review chapters authored by leading experts in the field, covering all the known human oncogenic viruses and malignancies that are associated with AIDS and NADM. There are a total of nine comprehensive chapters; one chapter is on HIV/AIDS malignancies; two chapters on KSHV and KS; one chapter is on EBV and associated lymphomas. There are three chapters on HPV and its associating cancers, head and neck squamous cell carcinomas and oral cancers, the anal cancer, and cervical cancers. There is one chapter on MCPyV and Merkel cell carcinomas, and one chapter on HBV/HCV and hepatocarcinomas.

The chapter by Pyring provided a comprehensive review on the current status of AIDS/HIV associated malignancies and their associating viral etiological agents. There are two chapters on KSHV and KS. The first is by He et al. The authors provided a comprehensive review on the molecular biology of KSHV, the regulation of the viral gene expression, the host immune response against the virus infection, and the mechanisms of cellular transformation and tumorigenesis. The second KSHV chapter by Dittmer and Damania described the KSHV and its associate diseases. It also described the prevalence of infection, the molecular biology of the virus and the disease, and its treatment. The chapter on EBV and lymphomas by Lang et al provided a comprehensive review of EBV, its molecular biology and the regulation of viral and cellular gene expression in EBV-associated lymphomas. It also described the various types of lymphomas associated with EBV and its association with HIV infection. There are three chapters on the three cancers associate with HPV. The first chapter is on HPV associate cervical cancer by Du; it described the biology of HPV and the global burden of cervical cancer, and co-infection by HIV in women. It also reviewed the risk factors involved, screening for cervical cancers, and prevention of HPV infection. The second chapter on HPV is by Hagansee on oral cancer. It described the risks, the prevalence and prevention of the cancer. It also described the molecular mechanisms that underlie HPV-mediated oncogenesis to lead to cancer. The third chapter on HPV and anal cancer is by Wang and Polefsky who reviewed the current literatures on anal cancers, the virus, the epidemiology, the clinical characteristics, the prevention, as well as the treatment and outcome of the cancer. The chapter by Caprio on Merkel cell carcinoma reviewed the clinical disease, its etiological agent and the gene regulation of the virus and changes in the tumor at the molecular levels. Finally, the chapter by Hu et al on HBV/HCV liver cancers reviewed the epidemiology of HBV/HCV and HIV co-infections; also on the possible mechanisms of hepatocarcinogenesis as well as the management of the cancer. It also discussed the other hepatitis virus, the HGV.

AIDS-Associated Malignancies

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Ramya Vangipuram and Stephen K. Tyring

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Abstract

Malignancies were one of the earliest recognized manifestations that led to the description of the acquired immune deficiency syndrome (AIDS). The majority of cancers in AIDS patients are associated with coinfection with oncogenic viruses, such as Epstein–Barr virus, human herpesvirus 8, and human papillomavirus, with resulting malignancies occurring secondary to diminished immune surveillance against viruses and virus-infected tumor cells. Over 50% of AIDS lymphomas are associated with Epstein–Barr virus (EBV) and/or HHV8 infection. HHV8-associated diseases include Kaposi sarcoma (KS), primary effusion lymphoma (PEL), and multicentric Castleman disease (MCD). EBV is associated with several malignancies, including Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Coinfection with HIV and HPV is associated with an increased risk of various squamous cell carcinomas of epithelial tissues. HAART has significantly impacted the incidence, management, and prognosis of AIDS-related malignancies. In addition to changing the natural history of HIV infection in regard to incidence and survival, HAART has dramatically

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decreased the incidence of certain virally mediated HIV-associated malignancies such as KS and primary CNS lymphoma. The beneficial effects of HAART on these tumors are attributed to drug-mediated HIV suppression and immune reconstitution. However, HAART has had a less favorable impact on EBV- and HPV-related malignancies. This chapter presents an overview of HIV-associated malignancies mediated by HHV-8, EBV, and HPV, and reviews the effect of HAART on the epidemiology, presentation, treatment, and outcomes of these cancers.

Keywords
Human herpesvirus 8 · Epstein–Barr virus · Human papillomavirus
Human immunodeficiency virus · Kaposi sarcoma · AIDS-associated lymphoma · Anogenital cancer

1.1 Introduction

Malignancies were one of the earliest recognized manifestations that led to the description of the acquired immune deficiency syndrome (AIDS). The rising incidence of Kaposi sarcoma in young homosexual men, a rare skin cancer typically seen in elderly men of Eastern European and Mediterranean descent, was a harbinger of the AIDS epidemic in the early 1980s. This was followed by sporadic reports of high-grade B-cell non-Hodgkin's lymphoma (NHL), primary cerebral lymphoma, and systemic NHL. By 1985, both Kaposi's sarcoma and high-grade B-cell NHL were classified as "AIDS-defining" illnesses by the Centers for Disease Control (CDC). In subsequent years, the CDC listed invasive cervical cancer as an AIDS-defining illness, given its poorer prognosis in HIV-positive women. Research later showed that the majority of cancers in AIDS patients were associated with coinfection with oncogenic viruses, such as Epstein–Barr virus, human herpesvirus 8, and human papillomavirus, with resulting malignancies occurring secondary to diminished immune surveillance against viruses and virus-infected tumor cells.

Over 50% of AIDS lymphomas are associated with Epstein–Barr virus (EBV) and/or HHV8 infection. HHV8-associated diseases include Kaposi sarcoma (KS), primary effusion lymphoma (PEL), and multicentric Castleman disease (MCD). EBV is associated with several malignancies, including Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). EBV is also implicated in cases of leiomyosarcoma, cervical, and anal cancer in patients with AIDS.

HAART has significantly impacted the incidence, management, and prognosis of AIDS-related malignancies. In addition to changing the natural history of HIV infection in regard to incidence and survival, HAART has dramatically decreased the incidence of certain virally mediated HIV-associated malignancies such as KS and primary CNS lymphoma. The beneficial effects of HAART on these tumors are

attributed to drug-mediated HIV suppression and immune reconstitution. However, HAART has had a less favorable impact on EBV-related malignancies; NHLs remain the most common tumors in the HAART era. This chapter presents an overview of HIV-associated malignancies mediated by HHV-8, EBV, and HPV, and reviews the effect of HAART on the epidemiology, presentation, treatment, and outcomes of these cancers.

1.2 Gammaherpesvirus-Associated Malignancies

The human gammaherpesvirus family includes Epstein–Barr virus (EBV) and human herpesvirus (HHV8), previously known as Kaposi sarcoma-associated herpesvirus (KSHV). Gammaherpesviruses establish a persistent infection, especially in lymphoid cells. In the immunocompetent host, the clinical course is usually asymptomatic. In immunocompromised hosts, such as post-transplant patients on immunosuppression and HIV-infected patients, both EBV and HHV8 are implicated in the development of a wide range of lymphoproliferative disorders.

A. Human Herpes Virus-8-Related Tumors

HHV8 was first isolated from Kaposi sarcoma lesions in patients with AIDS by Chang and Moore in 1994 [1], and subsequent studies demonstrated its association with other lymphoproliferative disorders in this population [2, 3]. Human herpesvirus-8 virus is the etiologic agent of three AIDS-associated malignancies: Kaposi sarcoma, a plasmablastic variant of multicentric Castleman disease (HHV8-MCD), and primary effusion lymphoma. Unlike other herpesviruses, HHV8 is not ubiquitous: while HHV8 is highly prevalent in sub-Saharan Africa (>50%), it is quite rare in most European countries, Asia, and the United States (seroprevalence rate <10%) [4, 5]. The prevalence is elevated in men who have sex with men (MSM) [6–8]. HHV8 is mainly transmitted via saliva [9], and sexual risk factors are probably a surrogate marker for close physical contact [10, 11].

Five clinical variants have been described: classic, endemic, iatrogenic, AIDS-associated (epidemic), and non-epidemic KS [12]. Classic KS describes an indolent cutaneous disease among elderly men of Mediterranean, Eastern European (Ashkenazi) Jewish, and South American origin. Endemic KS is an aggressive HIV-unrelated form that is commonly seen in sub-Saharan Africa, and often presents with visceral involvement. Iatrogenic KS is seen in patients receiving immunosuppressive drugs, particularly those with solid-organ transplants [13]. KS was one of the first manifestations of the HIV/AIDS epidemic in the 1980s. Recently, non-epidemic KS was proposed as a fifth subtype in patients who are at high risk for HIV, but are HIV seronegative [12].

1. AIDS-Associated KS

The introduction of HAART in the mid-1990s has led to a significant reduction in the incidence of KS in developed countries. However, KS is still the most common AIDS-defining malignancy in parts of sub-Saharan Africa where the seroprevalences of both HIV and HHV8 are high. AIDS-related KS exhibits a wide spectrum of clinical presentations. KS is staged using the AIDS clinical trials group modified staging classification (Table 1.1). The prognosis depends on the stage of KS, the level of immunosuppression, and the response to anti-HIV therapy. HAART results in a decrease in the incidence of KS.

KS is a multicentric angioproliferative spindle cell tumor arising from HHV8-infected lymphatic endothelial cells. While HHV8 is the etiologic agent of KS, HIV-induced immunosuppression is also an important cofactor in the induction of this malignancy. Both absolute decreases in CD4+ counts and lack of HHV8-specific T-cell immunity are associated with KS [14, 15]. In addition, KS is independently associated with the degree of HIV viremia [16]. Before the widespread use of HAART, patients coinfected with HIV and HHV8 were estimated to be 400–2000 times more likely to develop KS than those with just HHV8 infection [17]. The implementation of HAART in the United States and Western Europe resulted in an initial 80% decrease in the incidence of KS [18]. However, further decreases after 2000 have been more modest, and KS remains the second most common tumor arising in HIV-infected persons in the United States, after non-Hodgkin lymphoma, with a cumulative incidence of approximately 2% in the HAART era [19].

KS lesions may involve the skin, oral mucosa, lymph nodes, and visceral organs, especially the pulmonary and gastrointestinal tract. Most patients present with painless cutaneous lesions, which may have a macular, papular, nodular, or plaque-like appearance. Lesions can range in color from pink to red or purple and in size from several millimeters to large confluent areas. Lesions are typically localized in the oral cavity, on the face, and lower extremities, but can involve almost any site. Visceral disease sometimes occurs in the absence of skin lesions.

Table 1.1 AIDS clinical trials group modified staging classification

TIS staging of KS	Good risk (all of the following)	Poor risk (any of the following)
Tumor (T)	Confined to skin, lymph nodes, or minimal oral disease	Tumor-associated edema or ulceration, extensive oral KS, gastrointestinal KS, KS in other non-nodal viscera
Immune status (I)	CD4 cell count >150 cells/uL	CD4 cell count <150 cells/uL
Systemic illness (S)	Karnovsky performance status >70	Karnovsky performance status <70 or other HIV-related illness

Oral lesions may lead to ulceration, dysphagia, and secondary infection. Gastrointestinal KS has been described in almost half of patients at the time of initial diagnosis [20]. Gastrointestinal involvement is often asymptomatic; however, bleeding, perforation, and obstruction may occur [21]. Pulmonary KS is more frequent among patients with extensive cutaneous disease and more advanced immunosuppression, though 15% of patients with pulmonary KS have no mucocutaneous lesions at diagnosis [22]. In contrast to KS at other visceral sites, pulmonary KS is frequently symptomatic, and patients may present with bronchospasm and/or dyspnea, which may be life-threatening [22].

AIDS-associated KS is staged by the classification developed by the AIDS Clinical Trials Group (ACTG) Oncology Committee [23]. This classification utilizes three variables: tumor extent (T), immune status (I), and systemic symptoms (S), which are classified as good risk (0) or poor risk (1). For tumor burden (T), poor risk (T_1) is defined by the presence of extensive cutaneous or oral disease, tumor-associated edema, ulceration or visceral disease; for immune status, poor risk (I_1) is defined by CD4+ <150 cells/μL; and for systemic illness, poor risk (S_1) is defined by the presence of other opportunistic infections, constitutional symptoms, or poor performance status. The ACTG staging system was developed and initially validated in the pre-HAART era. A survival analysis conducted after the introduction of HAART suggested that tumor extent and systemic illness, rather than CD4+ T-cell count were the most important predictors of survival [24]. It has been proposed that patients can be classified into two main risk categories: good risk (T_0S_0, T_1S_0, or T_0S_1) and poor risk (T_1S_1) [24]. The 3-year survival rate for patients at stage T_1S_1 is 53%, compared to the 3-year survival rates with T_0S_0, T_1S_0, and T_0S_1, which were 88, 80, and 81%, respectively [24].

The introduction of HAART has dramatically improved the overall survival of patients with KS. The incidence rate of KS declined from 15.2 per 1000 patient-years to 4.9 per 1000 patient-years after the introduction of HAART, with a relative risk (RR) for KS of 0.32 (99% confidence interval [CI] 0.26–0.4) in the HAART era compared with the pre-HAART era [25]. Effective control of HIV viremia with HAART is imperative in patients with AIDS-KS and in patients with limited KS, is often sufficient [26]. For HAART-naïve patients with early KS (T0), the administration of HAART alone was associated with disease regression in several studies [27, 28]. While there is some evidence that HIV protease inhibitors have specific anti-KS activity [29], most studies indicate that prevention or control of KS is related to the degree of control of HIV, rather than the specific HAART regimen utilized [30]. In addition to HAART, a wide variety of treatments appear able to inhibit KS growth, including antiretrovirals, cytotoxic chemotherapeutic agents, retinoids, thalidomide, and matrix metalloproteinase inhibitors [28–34].

2. HHV8-Associated Multicentric Castleman Disease

Castleman disease was originally described in 1956 as localized lymph node hyperplasia resembling a thymoma [35]. It is now understood to be not just a single disease but rather an uncommon, heterogeneous group of nonclonal

lymphoproliferative disorders, which have a broad spectrum of clinical expression. There are generally two clinical variants: either localized to a single lymph node (unicentric) or with systemic involvement (multicentric). Multicentric Castleman disease (MCD) presents with generalized lymphadenopathy, multi-organ involvement, systemic symptoms of fever, fatigue, weight loss, and carries the potential for malignant transformation [36]. HHV8 is the etiologic agent of a plasmablastic form of MCD that is observed in HIV patients. MCD was first diagnosed in two homosexual men with AIDS in 1985 [37]. In individuals with AIDS, MCD is linked with malignant transformation to non-Hodgkin's lymphoma at 15-fold higher rate than those without MCD [38]. Unlike KS, HHV8-MCD appears to be becoming more frequent with the widespread use of HAART [39].

The clinical presentation of HHV8-MCD includes intermittent fevers, night sweats, fatigue, cachexia, edema, along with lymphadenopathy and/or hepatosplenomegaly [40]. Nonspecific respiratory and GI symptoms are common as well. Common laboratory abnormalities include anemia, cytopenias, hypoalbuminemia, hyponatremia, hypergammaglobulinemia, and elevated inflammatory markers such as C-reactive protein (CRP) [41]. HHV8-MCD symptoms are mediated by certain cytokines, especially human IL-6, HHV8 vIL-6, and human IL-10 [41]. vIL-6 is believed to play an important role in pathogenesis of HHV8-MCD, which may be independent or complementary to that of human IL-6, through autocrine and paracrine mechanisms of action [42]. HHV8-MCD is diagnosed via biopsy, whereby affected lymph nodes demonstrate involuted germinal centers with hyperplasia of vasculature and expansion of HHV8-infected plasmablasts in the mantle zone of the follicles [43].

Patients may have a waxing and waning course with exacerbations and subsequent remissions. At times, symptom flares can be severe and fatal. Flares are typically associated with high HHV8 viral loads [44]. There is no single consensus definition of HHV8-MCD flare or symptomatic activity; however, the French ANRS (Agence Nationale de Recherche sur le SIDA Castleman B trial group) have described criteria to define an attack of HIV MCD, based on fever, a C-reactive protein greater than 20 mg/L in the absence of any other cause, and 3 of 12 additional clinical findings (Table 1.2) [45]. HHV8-viral load has at times been used to assess symptomatic patients with HHV8-MCD, although assays vary between groups, and elevated HHV8 viral load is not specific for HHV8-MCD [46]. CT imaging in patients with HHV8-MCD generally shows diffuse, symmetric adenopathy, and hepatosplenomegaly [43]. Hemophagocytic syndromes also have been described [43]. Concomitant KS is present in up to 70% of individuals [43].

There is no standard therapy for HHV8-MCD. HIV-positive patients with HHV8-MCD generally are treated with concurrent HAART in addition to various therapies such as immune modulators, chemotherapy, and antiviral agents [47]. Rituximab, an anti-CD20 monoclonal antibody, given alone or in conjunction with chemotherapy, is thought to confer a beneficial effect by eliminating reactive B-cells, thus depriving the HHV8-infected plasmablasts of proliferation and survival signals by breaking virus and cytokine-driven feedback loops with the

Table 1.2 French ANRS criteria for HIV MCD flare

1. Fever
2. Serum C-reactive protein level >20 mg/L in the absence of any other etiology
3. At least, three of the following symptoms:
– Peripheral lymphadenopathy
– Splenomegaly
– Edema
– Pleural effusion
– Ascites
– Cough
– Nasal obstruction
– Xerostomia
– Rash
– Central nervous system symptoms
– Jaundice
– Autoimmune hemolytic anemia

Table 1.3 Expression of EBV latent genes and association with lymphomas

Latency pattern	EBNA-1	EBNA-2	EBNA-3	LMP-1	LMP-2	EBER	Disease
Type I	+	−	−	−	−	+	Burkitt lymphoma, primary effusion lymphoma
Type II	+	−	−	+	+	+	Hodgkin lymphoma
Type III	+	+	+	+	+	+	Primary CNS lymphoma

reactive B-cells [48, 49]. However, rituximab is associated with exacerbations of cutaneous KS [50].

Human IL-6 is important to the pathogenesis of MCD, and the use of monoclonal antibodies directed against IL-6 (siltuximab) or its receptor (tocilizumab) has shown clinical efficacy in HIV-negative HHV8 negative MCD [51–53]. However, because vIL-6 is antigenically different from human IL-6, a potential role for siltuximab in the treatment of HHV8-MCD remains to be explored. While human IL-6 is elevated in HHV8-MCD and contributes to symptoms and disease pathogenesis, given the additional role of vIL-6 and other HHV8 genes, it is unknown whether antihuman IL-6 therapy alone will be sufficient.

Even though life expectancy in multicentric Castleman disease has improved in the HAART era, it continues to have a poor prognosis and an increased incidence of non-Hodgkin lymphoma in the HIV context. Infection, multi-organ failure, Kaposi sarcoma, non-Hodgkin lymphoma, and progressive multicentric Castleman disease were the most often reported causes of death [43].