Kaposi Sarcoma–Associated Herpesvirus-Associated Malignancies: Epidemiology, Pathogenesis, and Advances in Treatment

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Kaposi sarcoma associated herpesvirus (KSHV), a γ2-herpesvirus, also known as human herpesvirus-8, is the etiologic agent of three virally associated tumors: Kaposi sarcoma, a plasmablastic form of multicentric Castleman disease (KSHV-MCD), and primary effusion lymphoma. These malignancies are predominantly seen in people with acquired immunodeficiencies, including acquired immunodeficiency syndrome and iatrogenic immunosuppression in the setting of organ transplantation, but can also develop in the elderly. Kaposi sarcoma (KS) is most frequent in regions with high KSHV seroprevalence, such as sub-Saharan Africa and some Mediterranean countries. In the era of combination antiviral therapy, inflammatory manifestations associated with KSHV-infection, including KSHV-MCD, a recently described KSHV-associated inflammatory cytokine syndrome and KS immune reconstitution syndrome also are increasingly appreciated. Our understanding of viral and immune mechanisms of oncogenesis continues to expand and lead to improved molecular diagnostics, as well as novel therapeutic strategies that employ immune modulatory agents, manipulations of the tumor microenvironment, virus-activated cytotoxic therapy, or agents that target interactions between specific virus-host cell signaling pathways. This review focuses on the epidemiology and advances in molecular and clinical research that reflects the current understanding of viral oncogenesis, clinical manifestations, and therapeutics for KSHV-associated tumors.
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Kaposi sarcoma-associated herpesvirus (KSHV) was first isolated from Kaposi sarcoma (KS) lesions in patients with acquired immunodeficiency syndrome (AIDS) by Chang and Moore in 1994[1] and was later established to be the etiologic agent of KS in several epidemiologically distinct populations.[2–4] Subsequent studies showed it to be the etiologic agent of several lymphoproliferative disorders, including primary effusion lymphoma (PEL), a plasmablastic form of multicentric Castleman disease (KSHV-MCD), and large cell lymphoma arising in the setting of KSHV-MCD.[5,6] We will review clinical aspects of KSHV-associated malignancies, including risk factors for tumor development, the relationship with human immunodeficiency virus (HIV), rarer manifestations of KSHV infection, select KSHV-encoded genes implicated in oncogenesis, as well as clinical presentation and treatment approaches for KS, KSHV-MCD, and PEL.

KS was initially described in 1872 as a lower extremity tumor among elderly men by the dermatologist Moritz Kaposi, and this form, which develops in Mediterranean or Ashkenazi Jewish men, has been called *classic* KS. KS was subsequently noted to be a relatively common tumor in sub-Saharan Africa in the 1950s–1970s, prior to the HIV epidemic[7]. Later, an association with immunosuppressive drugs was reported[8].

In 1981 an unusual clustering of KS cases among young men who have sex with men (MSM) in the United States was a harbinger of the AIDS epidemic[9] and KS was considered an AIDS-defining malignancy

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by the Centers for Disease Control and Prevention.[10] AIDS subsequently was found to be caused by a newly discovered human retrovirus, HIV. Between 20%–50% of AIDS patients developed KS during the early epidemic in the United States (US). An epidemiologic clue to the origin of KS came from the observation that KS incidence was much higher in HIV-infected MSM than in other HIV risk groups (eg, injection drug users), leading to the hypothesis that KS was caused by a transmissible agent other than HIV that was better transmitted by sexual contact than by exposure to blood.[11] The nature of this putative agent was initially elusive. However, this mystery was solved in 1994 when a novel γ2-herpesvirus, KSHV, was discovered by representational difference analysis of KS lesions compared to normal skin.[1] Cases of PEL and KSHV-MCD also have been described in patients without HIV. KSHV is a necessary etiologic agent for KS based on epidemiologic studies demonstrating temporality and strength of association, as well as experimental and laboratory evidence confirming biologic plausibility.[12,13] KSHV is classified as group 1 biological carcinogenic agent, with sufficient evidence to link to carcinogenicity in humans, by the International Agency for Research on Cancer[14]. However, only a small percentage of KSHV-infected individuals develop KSHV-associated tumors; thus KSHV infection is not sufficient to cause oncogenesis.

EPIDEMIOLOGY OF KSHV INFECTION AND ASSOCIATED MALIGNANCIES

The incidence of KS largely mirrors KSHV seroprevalence, although KS risk is dramatically increased by HIV co-infection. Several epidemiologic patterns of KS have been described: *classic* KS, discussed above; *endemic* KS occurring in men and women in Africa and often occurring at a younger age; *epidemic* KS associated with HIV infection; and *iatrogenic* KS, generally seen in the setting of transplantation. In regions with access to combination antiretroviral therapy (cART), AIDS-associated KS incidence has decreased by up to 80% since its peak in the early AIDS epidemic,[15] largely due to improved control of HIV viremia and preserved $CD4^+$ T-cell counts and immune function. Nonetheless, KS incidence in patients on long-term cART remains markedly elevated compared to the general population, even in patients with preserved $CD4^+$ counts. Furthermore, despite decreased HIV incidence in the United States since the peak of the AIDS epidemic, there are still 50,000 incident cases of HIV per year in the US,[16] and there continues to be a high rate of KSHV infection in this population. KS represents a major public health problem in sub-Saharan Africa, where KSHV infection is endemic and resources to treat HIV/AIDS-related complications are limited. In some areas and countries in Africa, it is the most common tumor in men.[17]

KSHV Serologic Assays

KSHV seroprevalence has been estimated in several large population-based studies. The primary means of assessing for KSHV infection is antibody testing. KSHV has a large genome with more than 85 genes, most of which have the potential to be antigenic. In KSHV-infected individuals, antibody response to viral antigens is variable, with certain antigens such as latency-associated nuclear antigen (LANA) or the capsid antigen K8.1 eliciting strong responses. Intensity of immune response also may depend on HIV status, as well as the co-existence of a KSHV-associated malignancy.[18] Current serologic studies employ either immunofluorescent assays (IFAs)[19] or enzyme-linked immunoassays (ELISAs) against one or more KSHV-encoded latent and/or lytic proteins.[20,21] The sensitivity of these assays is variable, while the specificity is generally greater than 95%.[22] With ELISAs, the definition of KSHV-seropositivity based on a combination of tests for reactivity against a lytic (K8.1) and latent (LANA) antigen increases sensitivity while preserving specificity, and this approach generally performs well in epidemiologic studies. However, there is no US Food and Drug Administration (FDA)-approved diagnostic test for clinical purposes such as documentation of acute infection. Additionally, challenges exist related to a gold-standard confirmatory test for KSHV infection in subjects without a documented KSHV-associated malignancy or detectable KSHV in the blood or saliva.

In addition to limitations in the accuracy of IFA and ELISA assays, these assays are technically burdensome. Newer recombinant antigen-based serologic assays employing either a luciferase immunoprecipitation system against four KSHV antigens[23] or a magnetic-bead based multiplex assay using six KSHV antigens[18] recently have been developed. These newer assays appear to be dynamic across a wider range of antibody concentrations and have a higher sensitivity and preserved specificity compared to earlier assays. However, they are currently performed only in a few research laboratories, and require validation in additional populations.

Estimates of KSHV Seroprevalence in Different Populations

KSHV was established in populations of endemic areas in the distant past and appears to have migrated with humans as they colonized the world. Subtypes of KSHV defined on the basis of strain