INTRODUCTION: KAPOSI’S SARCOMA AND KSHV/HHV-8

In 1872, the famed Hungarian dermatologist Moritz Kaposi characterized an “idiopathic multiple pigmented sarcoma” which is now known as Kaposi’s sarcoma (KS).424 For most of its history, KS has been a rare, slowly progressing neoplasm affecting mainly elderly men of Mediterranean and Eastern European descent. KS was not typically fatal, and patients tended to live ten or more years with the condition, and die of other unrelated ailments.201 An abrupt increase in the number of cases of KS among previously healthy young homosexual men was first reported in 1981, ushering in a new era of aggressive, rapidly fatal KS.40,155,180,210,401 Since approximately 30% of AIDS patients presented with KS as their initial symptom of HIV infection, KS evolved into a defining characteristic of one of the most devastating infectious diseases in history.35,177

The progressive depletion of cell-mediated immunity and subsequent loss of immune function caused by HIV infection predisposes patients to an array of unusual malignancies.177,381 AIDS patients do not have higher incidence of the more common tumors of the breast, colon, or lung than the general population; rather, they exhibit a greatly increased frequency of cancers induced by oncogenic viruses such as Epstein-Barr virus (EBV), human papilloma virus (HPV), and Kaposi’s sarcoma-associated virus (KSHV), also known as human herpesvirus 8 (HHV-8).99,177,381 Impaired immune surveillance promotes a permissive environment for uncontrolled viral replication, the spread of virus to surrounding cells and
tissues, and contributes to the multistep process of tumorigenesis. In the case of AIDS-KS, interactions between immunosuppression, HIV, and KSHV are required for malignant progression. Although HIV infection is neither necessary nor sufficient for the development of KS, it is associated with a much higher frequency of KS and alteration of its natural course. The HIV epidemic in Africa along with the high prevalence of endemic KSHV infection in the general population has led to an alarming number of cases of KS and KSHV-associated diseases on that continent alone. With the recent advent of HAART (highly active antiretroviral therapy), the overall incidence of AIDS-associated neoplasms has declined; however, factors such as lack of access to treatment, noncompliance with treatment regimens, and the development of drug resistance all contribute to an elevated risk for KS in HIV-infected patients and ensure that KS will present a continuing major health problem for years to come. Understanding of the molecular biology of KSHV alone and in the context of HIV infection is crucial for the development of therapies to treat and prevent the associated pathological processes.

Discovery

In the 1920s, it was observed that KS occurred more frequently in East and Central Africa. The uneven geographical distribution led to the hypothesis that KS might be caused by an infectious agent. In 1990, a landmark epidemiological study from Beral et al. reported that KS was 20,000 times more likely to occur in people with HIV than in the general population. KS was more common in those who had acquired HIV sexually than in those who had acquired it via other routes. The incidence of KS was not related to age or race, but showed a definite geographical distribution, with the highest prevalence in the areas that were the initial foci of the AIDS epidemic. The accumulation of the epidemiological evidence suggested the involvement of a sexually transmissible agent in the development of KS, which in western countries had spread mainly among homosexual men. Several groups attempted to identify the unknown agent, and in 1994, Yuan Chang and Patrick Moore used representational difference analysis to identify two fragments of a previously unknown herpesvirus in a biopsy sample from an AIDS-KS patient, instigating a new era in KS research.

Diseases Associated with KSHV

Since its discovery, extensive studies have demonstrated an etiologic role for KSHV in the development of KS. The involvement of KSHV in the pathogenesis of KS is now widely accepted based on the following criteria: (1) KSHV genomes are detectable in all clinical forms of KS (classic, endemic, iatrogenic, and AIDS-related); (2) KSHV infection is highly associated with subjects at high risk for developing KS such as HIV-infected gay men;