Pathogenesis of AIDS-Related Kaposi's Sarcoma

The occurrence of Kaposi's sarcoma (KS) in patients with HIV infection is more than 7,000 times higher than in the non-HIV infected population. The reason for this association is unclear but may involve decreased immune surveillance as a result of the profound cellular immune deficiency caused by HIV, a sexually transmitted KS-inducing virus, whose KS-transforming capabilities may be enhanced by HIV, or a direct or indirect effect of HIV itself in susceptible individuals.

Introduction

Kaposi's sarcoma (KS) was first described in 1872 as a rare vascular tumor characterized by multiple skin nodules of the lower extremity, which was seen primarily in older men of eastern European or Mediterranean descent [1]. The tumor rarely involved visceral organs and generally had an indolent course. A more virulent, endemic form of KS was subsequently described in sub-Saharan Africa and involved younger men with cutaneous, lymphatic, and visceral involvement. It ran a more aggressive clinical course. Yet another group of non-HIV-infected patients with KS were those who received immunosuppressive therapy for organ transplantation or an autoimmune disease and in whom occasional spontaneous regression of lesions had been reported with withdrawal of immunosuppressive therapy. These various KS-affected populations suggested possible genetic, infectious, and immunologic underpinnings to the development of these tumors [2].

AIDS-Related KS

The recognition of KS in US male homosexuals in the early 1980s heralded the AIDS epidemic [3]. Early descriptions of AIDS suggested that as many as 50% of gay men with T-cell immune deficiency developed KS as one of their manifestations of AIDS. The proportion of patients with KS as the initial manifestation of AIDS has declined to approximately 11% in 1991 [4,5]. Several characteristics of this tumor, including its more aggressive clinical course; frequent involvement of lymph nodes, gastrointestinal tract, lung, and other viscera; and its almost exclusive early occurrence in the gay male AIDS population with other evidence of immune deficiency suggested that this tumor was more akin to the African variant of KS and likely was associated with a sexually transmitted agent. An additional feature of AIDS-related KS (AIDS/KS) that must be explained in any model of pathogenesis includes the fact that approximately 90% of AIDS/KS cases in the United States occur in homosexual men, and far fewer cases have been seen in women, intravenous drug users, or heterosexual males. Kaposi's sarcoma has also been described in homosexual males who are not HIV-infected [6]. While the number of HIV-infected women is lower than the number of men, the frequency of KS in women is relatively high in Africa and in women in western countries who have had sex with bisexual men, compared to those whose sexual partners are heterosexuals or intravenous drug users (3% vs 0.7%) [7].

These findings suggest that a sexually transmitted infectious agent likely is involved in the pathogenesis of KS and that this agent is more prevalent in US gay men and the general African population. The findings also suggest that androgens or other male factors may facilitate the development of this tumor.

Viral Etiology

The declining incidence of KS in the gay male population in the mid- to late 1980s as a result of increased awareness of HIV and the more widespread use of safe sex practices led to speculation that sexually transmitted infections may be associated with the development of this tumor. Declining incidence of cytomegalovirus (CMV) seropositivity in association with declining occurrence of KS led to speculation of a potential role for this virus in KS pathogenesis [8,9]. Cytomegalovirus was not consistently detected by in situ hybridization or other methods in KS tissue, however, and the
widespread prevalence of this virus in AIDS patients who do not have KS argue against the involvement of CMV in KS tumor development [10].

There also has been speculation about the potential role that other DNA viruses, such as an Epstein Barr-like virus (EBV) [11] and the human papilloma virus (HPV), may play in the pathogenesis of KS [12]. However, the fact these viral sequences have not uniformly been found in KS tumors suggests that infection with these viruses may be more coincidental than causative for KS. No clear evidence of the involvement of CMV, EBV, or HPV in the development of KS has yet been established.

**KS-Associated Herpesvirus**

Recently, using representational difference analyses, Chang and Moore have identified sequences of a unique gamma human herpesvirus, termed the KS-associated herpesvirus (KSHV), in high frequency in KS tissues from patients with AIDS [13]. These viral sequences, somewhat homologous to sequences of the herpes saimiri virus, which can induce lymphoma in monkeys, have been identified in more than 90% of KS biopsies from HIV-infected and uninfected individuals but not in uninvolved tissues from the same patients or from normal controls [14-16]. Sequences of KSHV also have been found in an unusual variant of non-Hodgkin's lymphoma in patients with AIDS (ie, body cavity lymphomas), in association with EBV [17]. However, the recent finding of KSHV-like sequences in patients with other dermatologic disorders and the loss of these particles in multiple passaged KS cell lines raises the possibility that this virus could be a passenger virus rather than a directly transforming one [18]. Determination of the exact role of KSHV in the pathogenesis of KS will require viral isolation and further characterization of the direct and indirect effects of this virus. However, detection of KSHV sequences in high frequency and specificity in patients with KS has led to renewed interest in the role of viruses in the development of tumors in the setting of immunosuppression and in the possible use of viral inhibitory agents in controlling tumor development and growth.

**Pathology**

Lesions of KS vary considerably in their clinical presentation and, to a lesser degree, in their histologic appearance. These lesions can involve predominantly the skin and oral mucosa, as well as a number of visceral organs, and can range in appearance from pink or red macules to dark blue and purple papules or nodules.

Histologically, KS lesions are characterized by intense neovascularization and the appearance of spindle cells, which are considered to be the tumor cells of KS. The spindle cells proliferate among characteristic slit-like spaces produced by the aberrant vascular structures. These cells have a low mitotic index and are euploid [19,20]. Fibroblasts, extravasated red blood cells, and inflammatory cells are mixed in with the spindle cells. The histologic characteristics of early and advanced KS differ in that the spindle cells in advanced lesions are more abundant and form more compact masses.

The origin of the spindle cells is somewhat controversial, as these cells share several histologic features with various other types of cells [21]. Immunohistochemically, spindle cells are somewhat similar to endothelial cells in that they stain with *Ulex europaeus* and are negative to factor VIII and EN-4 [22]. A mesenchymal origin is suggested by the presence of alpha-actin, a smooth muscle marker, and shared positivity with the hematopoietic cell markers CD34 and CD18 [23]. It is currently believed that KS most likely is of mesenchymal origin, possibly a smooth muscle progenitor, with multiphenotypic markings reflective of early differentiation or transformation.

**Role of Cytokines in Growth Regulation of KS**

The ability to grow KS in vitro requires the presence of soluble factors which were initially identified in cultured supernatants from retrovirally infected T-cells and monocytes [24-26]. Subsequently, it has been shown that a number of known cytokines promote the growth and differentiation of KS cells in vitro. These include interleukin-1a (IL-alpha) and interleukin-1 beta (IL- beta, platelet-derived growth factor (PDGF), tumor necrosis factor- alpha (TNF- alpha), tumor necrosis factor- beta (TNF-beta), transforming growth factor- beta (TGF- beta), fibroblast growth factors (FGFs), interleukin-6 (IL-6), and oncostatin-M (Onco-M) [25,27-34].

Combinations of some of these cytokines have been shown to promote the growth of KS more effectively than individual cytokines [29]. Many of these cytokines are secreted by HIV-infected cells and are produced in high quantities during active HIV replication or as a result of other infections or inflammation. Antibodies to IL-1, basic fibroblast growth factor (bFGF), and PDGF and antisense oligonucleotides to IL-6 can inhibit KS cell growth [35]. Several cytokines, such as IL-1, TNF- alpha,
and IL-6, appear to have a more specific effect on KS-derived cells than on normal endothelial cells or fibroblasts [29]. This would suggest that the primary effect of these cytokines is to enhance the growth of tumors once they have been transformed by another, potentially infectious, agent [25]. Kaposi's sarcoma cells themselves also actively secrete a number of cytokines. High levels of bFGF, IL-1 beta, PDGF, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-6 have been detected in cultured KS cells [22,29,31,34-36,40]. These cytokines have a variety of paracrine and autocrine effects that lead to the development of lesions with histologic features similar to KS. Experiments involving inoculation of KS cells into nude mice or onto cultures of chick chorioallantoic membranes result in lesions with considerable neoangiogenesis [26,37,53]. An FGF-like activity has been detected in the culture supernatants of KS cells, which may synergize with other cytokines, such as IL-1 and IL-6 [30]. Similarly, KS supernatants can maintain the growth of spindle cells in vitro, demonstrating the autocrine nature of several of these secreted growth factors.

Synergy between various known KS-produced growth factors and the HIV tat protein has also been demonstrated in vivo [38,39]. HIV-1 tat gene expression in transgenic mice has been shown to induce endothelial proliferation and tumor development [52]. Modulation of IL-6 production and receptor expression may be the final pathway by which several cytokines, such as TNF-alpha, IL-1, and Onco-M; the tat gene product; and high-dose interferon-gamma exert their growth-promoting effect on KS [25,40].

Interleukin-6 is a cytokine normally produced by endothelial and mesenchymal cells. It has pleiotrophic effects, including effects on angioproliferation [41] and inhibition of apoptosis. Maintenance of KS cell growth in vitro with IL-6 has been clearly demonstrated [40].

Oncostatin-M

Oncostatin-M, which was initially identified due to its ability to inhibit the A357 melanoma cell line, has a variety of growth regulatory effects in both normal and malignant cells. It is the principle protein found in supernatants of activated retrovirally infected lymphocytes, and can stimulate the proliferation of KS cells, including induction of morphologic changes to spindle-shaped cells, while having no effect on normal human aortic smooth muscle cells or endothelial cells [32,33]. Antibodies to Onco-M can inhibit the stimulatory effects of exogenous oncostatin-M on spindle cells but have little effect on KS cells themselves [33]. Antisense to IL-6 decreases, but does not prevent, the growth-stimulating effects of Onco-M on KS. Interleukin-6 receptors and Onco-M receptors share a glycoprotein-134B subunit, which can convert low-affinity leukemia inhibitory factor (LIF) receptors to high affinity Onco-M receptors [42]. Regulation of the alpha-chain of the receptor may help determine the differential response of cells to IL-6 or Onco-M, and may be altered by a KS-inducing virus or other agents. These in vitro findings of the growth-promoting effects of various cytokines on KS may account for some of the variations seen in the clinical course of this tumor.

Cytokine Levels After Opportunistic Infections

After opportunistic infections, high levels of TNF-alpha, IL-1 alpha, and IL-6 are produced and may account for the development and rapid growth of KS after such infections. High levels of IL-6 have been found in patients with epidemic KS, and may precede these tumors in HIV-infected men [43]. A reduction in IL-6 level also has been reported in patients whose KS tumors respond to recombinant interferon- alpha [44]. Interferon- alpha has also been shown to have antiangiogenesis properties and may inhibit the effects of bFGF [45]. Apolipoprotein E, which is a component of high-density lipoprotein, has also been shown to inhibit angiogenesis associated with KS, and may be useful in inhibiting KS cell growth [46]. The mechanism of its effects in this tumor is currently under investigation.

Tumor Clonality and Hormone Sensitivity

Early findings of chromosomal abnormalities and oncogene expression in KS have not been confirmed or universally accepted [22,47]. Reports have described a "KS oncogene," which may belong to the FGF family [47]. The presence of Int-2, a factor expressed during embryonic development and which has transforming potential, has been identified in one report but not in another [48,30].

Recently, a clonal HIV-infected macrophage has been identified in one of four KS lesions, and was found to produce high levels of HIV tat, bFGF, and IL-6 [49]. This has led to the proposal of a "sequential" oncogenic process, in which clonal macrophages provide a growth factor milieu for stimulating the proliferation of responding cell populations that ultimately become autonomous. The fact that not all tumors have clonal HIV-infected macrophages suggests that this process perhaps
may be involved in early pathogenesis and that subsequent changes occur in the transformed KS cells, which may give rise to more autonomous tumor growth [49]. Recent studies evaluating the role of exogenous steroid hormones have shown that glucocorticoids [50], as well as androgens, have marked stimulatory effects on KS. A retrospective study of 62 HIV-infected men with and without KS has also shown that patients with KS have higher levels of dihydroepiandosterone and testosterone [51]. In contrast, tumor regression has been observed during pregnancy in HIV-infected women. The difficulty of growing KS in pregnant nude mice has suggested that female sex hormones may have inhibitory effects on this tumor. The inhibitory effect of human beta-chorionic gonadotropin (beta-HCG) on cultured tumor cells and on tumor growth in mice has been demonstrated [54]. Clinical studies of exogenously administered beta-HCG in humans with KS are in progress [55].

**Model of KS Pathogenesis**

A possible model for the development of KS is depicted in Figure 1. This model presupposes the existence of a sexually transmissible KS-associated virus that can infect and transform normal mesenchymal cells to a "pre-KS" cell or a primed KS progenitor cell. Infection of these mesenchymal cells may result in alteration of cell-surface receptors to a variety of cytokines. The presence of high levels of KS growth-stimulating cytokines, such as IL-6 and Onco-M, either as a result of widespread HIV infection or more localized production by "clonally infected" macrophages, would stimulate these cytokine receptors and trigger morphologic transformation to spindle-shaped cells. Further production of these cytokines by HIV-infected cells and the production of autocrine and paracrine factors locally by stimulated KS cells would lead to further proliferation and differentiation of the KS tumor. The HIV tat gene product, IL-6, TNF-alpha, IL-1, and other growth-promoting factors produced as a result of HIV infection or opportunistic infections also continue to stimulate tumor growth.

Androgens could help modulate the production of critical proteins, possibly via an IL-6 dependent pathway, which may account for the higher frequency of KS in men than in women. The circulation of KS cells in the blood or local deposition of clonally active HIV-infected macrophages may explain the multifocality of this disease. HIV induces greater immunosuppression, allowing continued growth of the tumor. As the tumor enlarges, KS may become autonomous in its growth and more akin to a true malignancy.

With greater understanding of the pathogenesis of KS and the role of KSHV, HIV, and various host immunologic and endocrinologic factors in its development, new directions for treatment will likely be forthcoming. Inhibition of KSHV, inhibition of cytokine production or blockade of cytokine receptors, as well as the use of antiangiogenesis compounds and modulation of intracellular signal transduction pathways, may ultimately lead to more effective, potentially less toxic treatments and prevention of this tumor.

**References:**


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