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PATHOGENESIS OF AIDS-ASSOCIATED KAPOSI'S SARCOMA

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INTRODUCTION

The pathogenesis of Kaposi's sarcoma has remained an enigma since its original description by Moritz Kaposi over 100 years ago. A classic monograph 30 years ago by Bluefarb provided only limited insight on the subject. Today, we recognize at least three clinical settings in which Kaposi's sarcoma occurs: the "classical" type, which afflicts elderly men of Eastern European and Mediterranean origin; the "endemic" type which occurs predominantly in Central Africa; and the "epidemic" type associated with iatrogenic or acquired immunodeficiency (1). The gross appearance, anatomic location, and natural history of the neoplasm varies considerably in each setting, although the histological picture remains remarkably consistent.

The histological hallmark of Kaposi's sarcoma is the spindle cell, accompanied by varying numbers of endothelioid mesenchymal cells which tend to form vascular slits. Admixed are inflammatory cells (particularly plasma cells), erythrocytes, and fibrous tissue. Despite general agreement that Kaposi's sarcoma is a vasoformative tumor, the precise histogenesis of the tumor remains in dispute. The emergence of cellular phenotypic markers using monoclonal antibodies and their application to tissue sections will help to resolve the issue. At present, the most tenable hypothesis is that Kaposi's sarcoma derives from endothelial cells that comprise venous-lymphatic anastomoses (2).

Oncogenesis

A recent set of discoveries has provided considerable insight into the molecular genetics of oncogenesis that bear on my hypothesis. Proto-oncogenes are DNA sequences that control normal cell growth and differentiation. The process of neoplasia is accompanied by enhanced copy number or expression of these genes, whose products have either nuclear or cytoplasmic actions. We presume that the phenomenon of oncogene activation, which occurs in nature by chromosomal translocations or by mutation, is a driving force in tumorigenesis. Finally, oncologists agree that cancer development is a stepwise phenomenon that requires participation of families of oncogenes over extended periods of time (3,4).

Pathogenesis of AIDS

The discovery of the human immunodeficiency virus (HIV) and its specific tropism for the CD4 receptor on helper lymphocytes has opened broad avenues of research on the pathogenesis of AIDS. Despite unprecedented progress, including the identification of a drug that slows replication of the virus, we still do not understand exactly how the immune deficiency of AIDS occurs.

Immunologic studies disclose a progression of illness after initial HIV infection that is characterized by the following stages: B cell hyperplasia with lymphadenopathy and hypergammaglobulinemia; slow decline of CD4 lymphocyte levels; involution of lymph nodes showing "follicle lysis"; gradual reduction of antigen processing cells (Langerhans cells, dendritic cells, macrophages); and a final stage of lymphoid atrophy with severe lymphopenia accompanied by a wasting syndrome. Other manifestations, such as neuro-psychiatric illness, may dominate the clinical picture. Many stages or classifications of HIV infection have appeared in the literature that generally describe this course.

Space limitations preclude an extensive discussion of the pathogenesis of AIDS. Basically, there are two interacting mechanisms at work. One clearly evolves from the virus infection itself and the elaboration of viral proteins. Because HIV RNA can be detected in only 0.01% of peripheral blood lymphocytes, direct viral cytopathology is an unlikely mechanism for progressive destruction of lymphocytes and macrophages. Recent work has shown that the HIV envelope, gp120, interacts with the CD4 receptor of "helper" lymphocytes and monocytes to cause cell fusion and death, even in uninfected cells. This viral protein may also play a role in the pathogenesis of the neuropathic manifestations of AIDS.

There are certainly host factors that contribute to the illness. Since HIV can productively infect lymphocytes (and latently infect macrophages), a successful immune response to the virus will impair or destroy the target cells. Further, HIV, in its selective attachment to the CD4 molecule, must mimic the shape of the normal ligand for CD4, namely the non-polymorphic portion of class II major histocompatibility antigen (MHC). Thus, both humoral and cellular immune responses to viral protein may cross-react with MHC on the surface of antigen presenting cells, producing steric blockade and possible cell damage. The anti-idiotypic response to HIV antibody would home to CD4 lymphocytes, further hindering lymphocyte-macrophage communication. These considerations have given rise to an autoimmune hypothesis that helps explain the immune abnormalities in AIDS. Other host factors to consider include a genetic predisposition, repeated immune stimulation, and other phenomena that alter immunity (e.g., pregnancy, immunologic immaturity, malnutrition) (5).

Main features of AIDS-associated Kaposi's sarcoma

Several remarkable features characterize Kaposi's sarcoma in persons with AIDS. First, in the USA it is most common among homosexual men (40% of cases) with declining incidence in intravenous drug users (10%), and children (3%). Inexplicably, the incidence of AIDS-associated Kaposi's sarcoma has slowly declined in the last two years so that it represents about 20% of cases. We may infer from these observations that there are cofactors peculiar to Kaposi's sarcoma in homosexual men, and that these cofactors have changed over time (2).

Second, the tumor appears in odd anatomic locations. In the skin, it is often bilaterally symmetrical. Kaposi's sarcoma develops in sites of previous trauma, and involves lymph nodes and visceral organs (mainly the gastrointestinal tract and lungs) as the disease progresses. Clearly these phenomena imply that local factors, possibly vascular or neural, influence the distribution of tumor.

Third, selected Kaposi's sarcoma lesions may regress spontaneously. Indeed, some patients with HIV infection display minimal immune dysfunction and may live in symbiosis with their tumors for many years. A handful of homosexual men who display normal immune function have developed Kaposi's sarcoma in the *absence* of HIV infection. Sometimes, Kaposi's sarcoma heralds a rapid, devastating clinical course. Thus, the natural history of Kaposi's sarcoma

varies considerably, is influenced by host factors, and does not necessarily "march to its own drum".

Finally, treatment of patients with AIDS-associated Kaposi's sarcoma with radiotherapy, chemotherapy, or interferon, makes little difference in the overall clinical course. Although lesions regress in up to 60% of cases, it is the severity of the underlying immunodeficiency that becomes the final determinant of the patient's outcome.

Pathogenesis of Kaposi's sarcoma

To understand Kaposi's sarcoma, it is best to "think like an endothelial cell". These cells line all vessels: arteries, arterioles, capillaries, veins, and venules of the systemic circulation, and the lymphatic vasculature. Like virtually all other cells in the body, endothelial cells can become neoplastic.

A mesenchymal derivative, the endothelium is remarkably active during embryonic development, and upon micro-environmental demand, this pluripotential tissue becomes highly specialized (e.g., retina, placenta, kidney, brain). In the adult, under conditions of cyclic activity (e.g., menstruation), tissue repair (e.g., trauma), inflammation (e.g., infection or autoimmune damage) or neoplasia, the endothelium responds vigorously to physiologic stimuli, the so-called angiogenic factors. Thus, the endothelium is a versatile, adaptive, and dynamic tissue (2).

It seems reasonable to postulate that Kaposi's sarcoma, an endothelial tumor, owes its genesis to the influence of angiogenic factors. The field of angiogenesis has made major advances in recent years. In particular, the discovery of fibroblast growth factor (FGF), a potent endothelial cell mitogen, has provided a unifying explanation for angiogenic phenomena observed *in vitro*. Many so-called endothelial growth factors can now be related to basic or acidic forms of FGF (6).

Kaposi's sarcoma itself is a vascular tumor and likely responds to endothelial growth factors. Further, there is an intriguing link of endothelial cells to the immune system. For example, endothelium can express class II histocompatibility antigens and act as an antigen presenting cell. Endothelial proliferation accompanies inflammation and in some cases such as angiofollicular hyperplasia, may dominate the histologic picture. Since the early stages of AIDS are characterized by lymphoproliferation, it seems logical to posit that the humoral environment in lymph nodes and neighboring tissues stimulates endothelial cells. Such stimulation may derive from lymphokines (paracrine factors) or from the endothelial cells themselves (autocrine factors).

Evidence for elaboration of angiogenic factors in retrovirus-infected cell lines has been described. Kaposi's sarcoma cell culture growth has been stimulated by medium from lymphocytes infected with HTLV II (7). Interleukin-I, a lymphokine elaborated from stimulated monocytes, bears sequence homology to FGF. Other lymphokines also stimulate endothelial cell growth *in vitro*. Thus, it is reasonable to assume that stimulated lymph nodes and lymphatic channels contain high concentrations of angiogenic factors (2).

Another intriguing set of observations about nerve connections may help explain the unique anatomic distribution of Kaposi's sarcoma. Peripheral nerves elaborate substances that evoke proliferative tissue responses. Thus, sympathetic nerve fibres release vasoactive intestinal peptide that may regulate bone mineral resorption (8). Neurogenic release of substance P stimulates synoviocytes and may play a role in rheumatoid arthritis. It is fascinating in this regard that substance P bears sequence homology to FGF (9). This line of inquiry may lead to important connections between neurokines and tissue responses.

Finally, evidence is accumulating that Kaposi's sarcoma cells themselves display oncogene activity. In one experiment, DNA from Kaposi's sarcoma was transfected into NIH 3T3 cells which went on to form vascular tumors when injected into nude mice (10). In another

experiment, an oncogene that bears homology to FGF was discovered in Kaposi's sarcoma cells (11). Thus, it is possible that the neoplasm itself produces an autocrine growth factor.

SUMMARY

Kaposi's sarcoma presents the oncologist with a myriad of unanswered questions. What accounts for the genesis, distribution, and natural history of this tumor? How could a tumor with such a singular histologic appearance occur in such diverse clinical circumstances? What accounts for the unusual geographic, ethnic, and demographic features of Kaposi's sarcoma? Clearly, the answers to these questions will involve a multifactorial etiology, and may only be arrived at by methodical, piecemeal dissection of each question.

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