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Kaposis Sarcoma-Associated Herpesvirus

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Description

Kaposi's sarcoma (KS) is the most common neoplasm associated with AIDS. Initially described as a rare and indolent tumor of elderly Mediterranean men, it was later recognized to occur at a higher frequency in Africa. Still later, KS was documented among immunosuppressed organ transplant recipients. In all cases, the histologic picture of the disease is strikingly similar and highly distinctive. Unlike most tumors, which arise from the clonal outgrowth of a single cell, KS lesions contain many cell types. Advanced lesions contain a predominance of spindle-shaped cells (spindle cells), the histogenesis of which remains uncertain but which are believed to arise from endothelial cells (or a more primitive mesenchymal precursor of such cells). In addition, there are infiltrating mononuclear cells (including plasma cells and monocyte-macrophages) and a highly characteristic profusion of slit-like neovascular spaces.

The vascularity of the lesion gives KS its distinctive reddish or violaceous appearance. This complex histology sets KS apart from most other tumors and raises important questions about its pathogenesis. Based on the properties of spindle cells cultivated from AIDS-related KS specimens, many studies have pointed to a key role for growth factors and cytokines in the evolution of a KS lesion. In general, such cells are not fully tumorigenic: Most do not produce stable, transplantable tumors in nude mice or grow in soft agar. In fact, they are dependent on exogenous growth factors for their proliferation and, in turn, they produce an array of growth factors and angiogenic factors. When transplanted into nude mice, they survive only transiently, then involute. However, during their period of viability, they recruit host inflammatory cells and neovascular structures very reminiscent of KS. When the human spindle cells involute, the entire lesion disappears. This suggests a model for KS in which the proliferating spindle cells drive the rest of the lesion via the elaboration of growth and angiogenic factors.

The central question then is: What drives the proliferation of the spindle cells? One early model attempted to relate spindle cell growth to HIV infection. Certainly, HIV infection is an enormous risk factor for KS development: The prevalence of KS in AIDS patients is 20,000 times that in the general population and 300 times that observed in other immunosuppressed populations. However, both in vivo and in cell culture, spindle cells do not appear to carry the HIV genome, ruling out direct infection by HIV as the growth-promoting event. Rather, HIV infection is limited to the smaller lymphoid and mononuclear cell components of KS. Such HIV-infected cells can be shown in vitro to release factors that promote cultured spindle cell growth, including both cellular cytokines and the HIV tat gene product. These observations suggest a plausible mechanism by which HIV infection could drive KS lesion formation without directly infecting the spindle cell. However, doubts soon arose concerning the ability of HIV infection alone to account for the etiology of KS. First, of course, KS can certainly arise in HIV-negative hosts. More important, even within the HIV-infected population, large differences in KS risk are not accounted for by the preceding formulation. KS risk is highest in homosexual men with AIDS: A full 20% to 30% of such individuals will develop KS in the course of their HIV disease. By contrast, fewer than 1% to 2% of AIDS cases related to hemophilia (i.e., blood product administration) will be complicated by KS, and KS is rarer still among pediatric AIDS cases in which HIV infection is acquired vertically from infected mothers. These and other data suggest the possibility of a sexually transmitted cofactor in KS etiology or pathogenesis.

A polymerase chain reaction–based method to identify DNA sequences that were present in DNA extracted from an AIDS-KS specimen but absent from normal genomic DNA from the same patient. Two small DNA fragments emerged that were shown to be highly correlated with KS: Virtually all AIDS-KS tumors were positive for these sequences, whereas available tissue specimens from a large number of HIV-negative hosts were negative, as were most non-KS tissues from patients with KS. Interestingly, approximately 10% to 15% of lymphoid tissues from AIDS patients who did not have KS were also positive, indicating that the sequences track with both KS and the risk for KS development. Sequence analysis of these two small DNA fragments reveals homology to two known lymphotropic herpesviruses, human EBV and the simian herpesvirus saimiri (HVS). These seminal findings point to the existence of a novel herpesvirus, termed KS-associated herpesvirus (KSHV) or human herpes virus-8 (HHV-8), and suggest it as a candidate for the exogenous cofactor earlier predicted by epidemiologists.