

*Medical Progress***KAPOSI'S SARCOMA**

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IN 1872, Moritz Kaposi, a Hungarian dermatologist, described five men with aggressive "idiopathic multiple pigmented sarcomas of the skin."¹ One patient died of gastrointestinal bleeding 15 months after the initial appearance of the skin lesions, and an autopsy showed visceral lesions in the lungs and the gastrointestinal tract. Subsequently, other investigators described four clinical variants of Kaposi's sarcoma that had identical histologic features but developed in specific populations and had different sites of involvement and rates of progression (Table 1). In the light of recent discoveries regarding the viral pathogenesis of Kaposi's sarcoma, these variants most likely represent different manifestations of the same pathologic process.

**CLINICAL VARIANTS
OF KAPOSI'S SARCOMA****Classic Kaposi's Sarcoma**

The classic variant primarily affects elderly men of Eastern European and Mediterranean origin. Classic Kaposi's sarcoma is much more common in men than in women, with a ratio as high as 15 to 1. Multiple firm, purple-blue or reddish-brown plaques and nodules typically appear initially on the hands and feet and progress up the arms and legs over a period of years or decades, eventually involving the viscera or mucosa in about 10 percent of patients. Untreated lesions evolve from flat discolorations or patches to plaques and then to raised nodules that become confluent. Lymphedema may precede or follow the appearance of visible lesions. Characteristic histologic features include spindle-shaped tumor cells surrounding hyperemic vascular slits, often in association with

extravasated erythrocytes, hemosiderin, and fibrosis (Fig. 1).

The median age at histologic diagnosis in one study of 67 men and 23 women was 64 years (range, 26 to 90).² An increased risk of lymphoma has been observed in association with Kaposi's sarcoma in some studies but not others. Homosexual men may be at increased risk for classic Kaposi's sarcoma, even in the absence of clinically detectable immunosuppression.

Endemic Kaposi's Sarcoma

In the 1950s, Kaposi's sarcoma was recognized as being common in portions of Africa. Kaposi's sarcoma accounted for 3 to 9 percent of reported cancers in Uganda in 1971.³ In 1983, Bayley noted an abrupt increase in the incidence of Kaposi's sarcoma in Zambia. In addition to the usual number of patients with typical endemic Kaposi's sarcoma, he documented an increasing number of patients with an aggressive atypical variant that responded poorly to conventional treatment.⁴ Once the acquired immunodeficiency syndrome (AIDS) could be diagnosed reliably and patients could be classified as having human immunodeficiency virus (HIV)-negative endemic Kaposi's sarcoma or HIV-positive epidemic Kaposi's sarcoma, African centers distinguished between the two in reporting treatment results.

In a retrospective analysis of 47 HIV-negative black South African patients treated in the Johannesburg General Hospital between 1980 and 1990, 29 presented with localized disease.⁵ Four of the 47 had concurrent lymphoma.⁵ Typical findings in 10 Zambian men (median age, 41 years) with indolent disease were nodules or plaques on edematous limbs.⁴ None died of the disease in the short follow-up period. Kaposi's sarcoma in HIV-negative and HIV-positive patients is now the most frequently occurring tumor in central Africa, accounting for 50 percent of tumors reported in men in some countries.⁶ An aggressive lymphadenopathic Kaposi's sarcoma affects African children in particular.⁷ In eastern and southern Africa, Kaposi's sarcoma makes up 25 to 50 percent of soft-tissue sarcomas in children and 2 to 10 percent of all cancers in children.⁷

Immunosuppression-Associated, or Transplantation-Associated, Kaposi's Sarcoma

Another group at increased risk for Kaposi's sarcoma are organ-transplant recipients and patients who are receiving immunosuppressive therapy for a variety of medical conditions, particularly members of certain ethnic groups at increased risk for classic Kaposi's sarcoma.⁸⁻¹⁷ In a series of 2099 organ-transplant

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TABLE 1. VARIANTS OF KAPOSI'S SARCOMA.

VARIANT	RISK GROUP	MEDIAN SURVIVAL
Classic	Elderly men of Eastern European or Mediterranean origin	Years or decades
Endemic	African children and adults	Months or years
Immunosuppression-associated, or transplantation-associated	Organ-transplant recipients	Months or years
Epidemic, or AIDS-associated*	Persons infected with human immunodeficiency virus, especially homosexual or bisexual men	Weeks or months

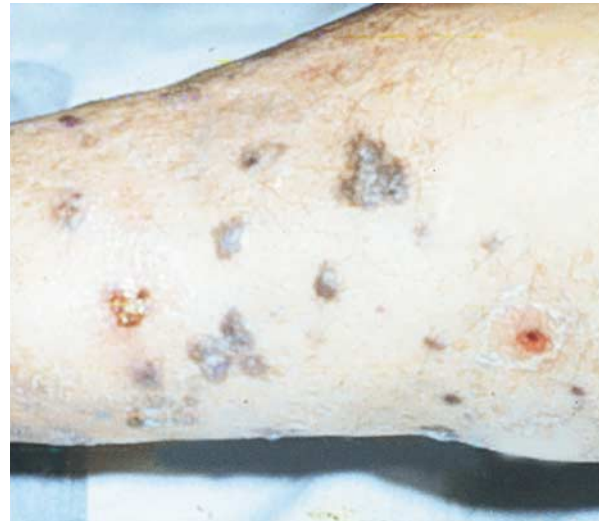
*AIDS denotes acquired immunodeficiency syndrome.

recipients studied at the Toronto Hospital, Kaposi's sarcoma developed in 12 (0.6 percent), 9 of whom were of Italian origin.⁸ The Collaborative Transplantation Research Group of Ile de France⁹ reported a 0.5 percent overall risk of Kaposi's sarcoma in 7923 organ-transplant recipients. In a series in Saudi Arabia, 14 cases of Kaposi's sarcoma (5.3 percent) developed among 263 patients who underwent transplantation between 1975 and 1986.¹⁷

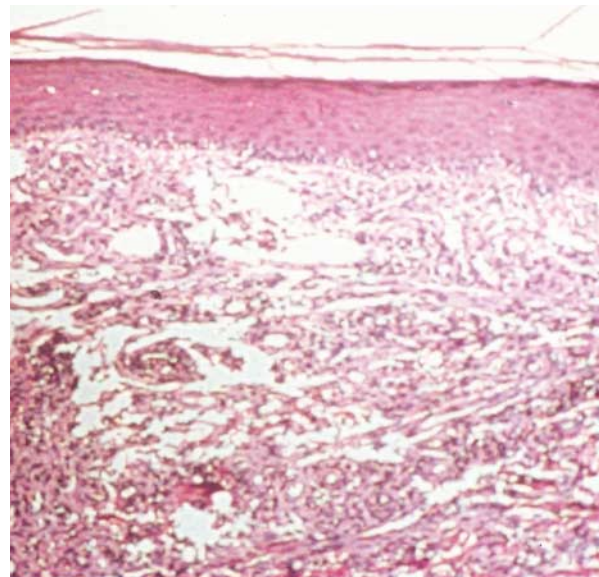
The median interval from organ transplantation to the diagnosis of Kaposi's sarcoma is 29 to 31 months (range, 3 to 124 months).^{13,14} In three series with a total of 35 cases of Kaposi's sarcoma, the percentage of men in whom Kaposi's sarcoma developed ranged from 67 percent to 80 percent, with a ratio of male to female patients ranging from 2:1 to 4:1.^{8,13,14} This type of Kaposi's sarcoma tends to be aggressive, involving lymph nodes, mucosa, and visceral organs in about half of patients, sometimes in the absence of skin lesions. The presence of concurrent lymphoma, tuberculosis, or transfusion-related HIV infection makes it difficult to diagnose Kaposi's sarcoma accurately.¹⁸⁻²⁰

Epidemic, or AIDS-Associated, Kaposi's Sarcoma

In 1981, Friedman-Kien et al. described more than 50 previously healthy, young homosexual men with Kaposi's sarcoma involving lymph nodes, viscera, and mucosa as well as skin.²¹ Concurrent life-threatening opportunistic infections were associated with a profound defect in cell-mediated immunity, a syndrome now recognized as AIDS. This aggressive and frequently fatal epidemic variant of Kaposi's sarcoma affected homosexual men with AIDS 20 times as frequently as it did male patients with hemophilia and AIDS who had similar degrees of immunosuppression.²² Although the incidence of Kaposi's sarcoma in American men with AIDS decreased from 40 percent in 1981 to less than 20 percent in 1992,²³ it remains the most common AIDS-associated cancer in the United States.



A



B

Figure 1. Kaposi's Sarcoma.

Panel A shows the lesions of classic Kaposi's sarcoma. Panel B shows the characteristic histologic features (hematoxylin and eosin, $\times 20$). The proliferation of spindle-shaped tumor cells has led to the formation of abnormal vascular slits, some of which contain red cells. Mitotic activity is absent in this lesion, and the degree of pleomorphism of the tumor cells is mild.

KAPOSI'S SARCOMA—ASSOCIATED HERPESVIRUS

Compelling epidemiologic evidence, including the peculiar geographic distribution of Kaposi's sarcoma, prompted speculation about an infectious cause as well as the possibility of sexual transmission.²² In 1994 Chang and colleagues identified DNA fragments of a previously unrecognized herpesvirus, which has

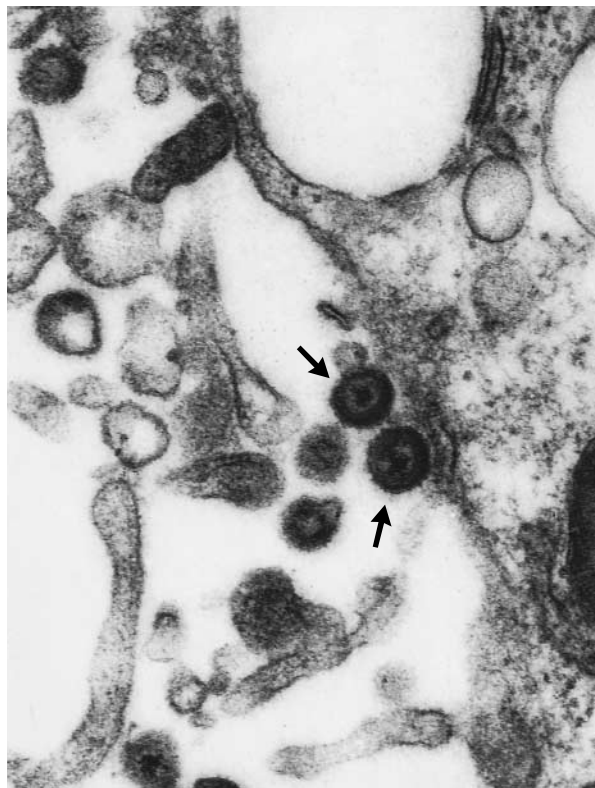


Figure 2. Kaposi's Sarcoma–Associated Herpesvirus. On electron microscopy, the size and shape of Kaposi's sarcoma–associated herpesvirus 8 virions (arrows) characterize them as members of the herpesvirus family ($\times 36,000$). (Courtesy of Antonella Tosoni, Ospedale Luigi Sacco, Milan, Italy.)

been called Kaposi's sarcoma–associated herpesvirus (KSHV, also known as human herpesvirus 8), in a Kaposi's sarcoma skin lesion from a patient with AIDS.²⁴ Over 95 percent of Kaposi's sarcoma lesions, regardless of their source or clinical subtype, have been found to be infected with KSHV (Fig. 2). Although studies have been published on the contribution of cytokines as well as HIV tat protein to the pathogenesis of Kaposi's sarcoma lesions, it is clear that the presence of KSHV is the primary and necessary factor in the development of this tumor. In addition, immunosuppression in the host appears to be an important cofactor in the clinical expression of Kaposi's sarcoma in some KSHV–infected patients. The relation between clinical lesions and immunosuppression underscores the unusual pathology and clinical course of this proliferative disease and suggests that Kaposi's sarcoma may not be a conventional neoplasm.

KSHV is the eighth human herpesvirus to be identified. Most human herpesviruses are associated with disease in immunocompromised hosts, as a result of either the reactivation of latent virus or the proliferation of growth-transformed cells. Herpesviruses

are divided into three subfamilies (Fig. 3), and both KSHV and Epstein–Barr virus (EBV) are members of the gammaherpesvirus subfamily.²⁵ Gammaherpesviruses are notable for causing tumors, particularly lymphoproliferative disorders and lymphomas in humans and animals. Molecular epidemiologic data suggest that KSHV may be an ancient pathogen of humans that has spread very slowly in the population.²⁶ Alternatively, the virus may have become pathogenic to humans more recently (within the past several thousand years), originating from a nonhuman primate host in Africa and slowly spreading to Mediterranean populations. In either case, any attempt to trace the origin and distribution of KSHV must take into consideration the more recent rapid intercontinental dissemination of the virus before and during the AIDS epidemic.^{27,28} KSHV appears to have spread from epicenters of AIDS in the United States to homosexual communities in Canada and Europe, suggesting that its appearance early in the AIDS epidemic actually represents an independent epidemic.²⁸

The 165-kb KSHV genome was sequenced within two years after its discovery,²⁹ which provided important clues about the way in which this virus might induce uncontrolled cellular proliferation. Unlike most other viruses, KSHV incorporated several recognizable host-cell genes during its evolution (Fig. 4). This molecular piracy facilitates studies of KSHV, since the viral genes can readily be compared with their cellular counterparts. For example, the virus encodes proteins that are homologous to human oncoproteins, including a cyclin that inhibits the retinoblastoma protein, which controls the G1-to-S phase of cell growth,³⁰ and a Bcl-2–like protein that prevents apoptosis.³¹ Other regulatory KSHV proteins include a G-protein–coupled receptor,³² an inhibitor of apoptosis mediated by the FLICE (Fas-associated death domain–like interleukin-1 β –converting enzyme) pathway,³³ a constitutively active immunoreceptor,³⁴ and an inhibitor of the interferon signaling pathway,³⁵ all of which may disrupt the control of cellular proliferation. KSHV also encodes an interleukin-6 and three functional chemokines that can be secreted by infected cells and that affect the replication and migration of uninfected cells.³⁶ The viral cytokine interleukin-6 induces B-cell proliferation, whereas the chemokines may activate angiogenesis and inhibit the immune type 1 helper-T-cell responses.³⁷ Recently, Friberg et al. demonstrated that the major latency-associated nuclear antigen (LANA) can interact with p53 and inhibit transcriptional activity mediated by p53.³⁸

Although KSHV encodes genes that clearly have the molecular potential to induce cellular proliferation and prevent apoptosis, current research is oriented toward discovering which genes are active in specific human tumors. Preliminary studies of a number of KSHV proteins suggest that there are differences in expression depending on the type of cell infected

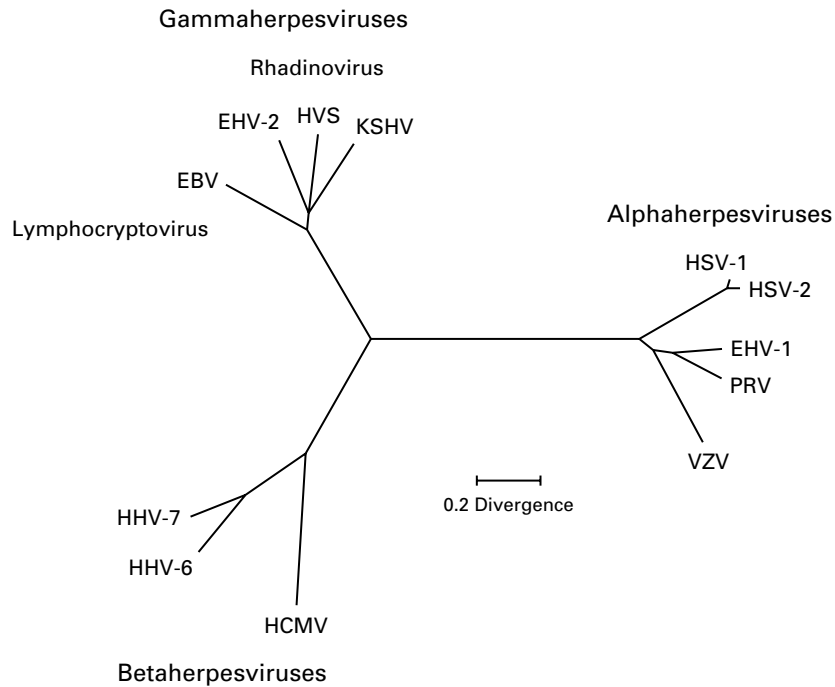


Figure 3. Phylogenetic Tree of Known Human Herpesviruses as Well as Several Other Herpesviruses That Have Nonhuman Hosts.

The tree was derived by comparing the amino acid sequences of the major capsid protein gene. Kaposi's sarcoma-associated herpesvirus (KSHV) is a member of the subfamily of gammaherpesviruses, genus rhadinovirus. EBV denotes Epstein-Barr virus, EHV-2 equine herpesvirus type 2, HVS herpesvirus saimiri, HSV herpes simplex virus, HSV-1 herpes simplex virus type 1, HSV-2 herpes simplex virus type 2, EHV-1 equine herpesvirus type 1, PRV pseudorabies virus, VZV varicella-zoster virus, HCMV human cytomegalovirus, HHV-6 human herpesvirus 6, and HHV-7 human herpesvirus 7. Adapted from Moore et al.²⁵ with the permission of the publisher.

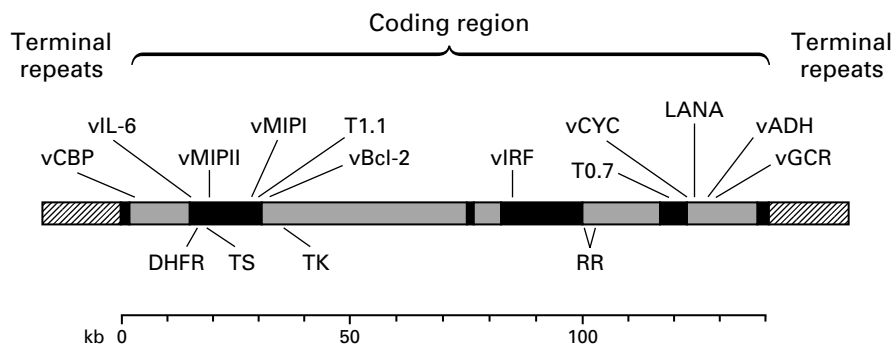


Figure 4. The 165-kb Kaposi's Sarcoma-Associated Herpesvirus (KSHV) Genome.

The entire coding region is flanked by terminal-repeat sequences (hatched boxes). The gene encodes numerous proteins that are homologous to cell-signaling and regulatory-pathway proteins found in human cells (solid boxes) and that are unique to KSHV and related rhadinoviruses. The proteins encoded include viral complement-binding protein (vCBP), viral interleukin-6 (vIL-6), viral macrophage inflammatory protein type 1 (vMIPI) and type II (vMIPII), viral Bcl-2 (vBcl-2), viral interferon regulatory factor (vIRF), viral cyclin (vCYC), latency-associated nuclear antigen (LANA), viral adhesin (vADH), G-protein-coupled receptor (vGCR), dihydrofolate reductase (DHFR), thymidylate synthase (TS), thymidine kinase (TK), and ribonucleotide reductase (RR). Stippled boxes indicate regions that are homologous to those of other herpesviruses. T1.1 and T0.7 denote nonhomologous open reading frames with undetermined activities.

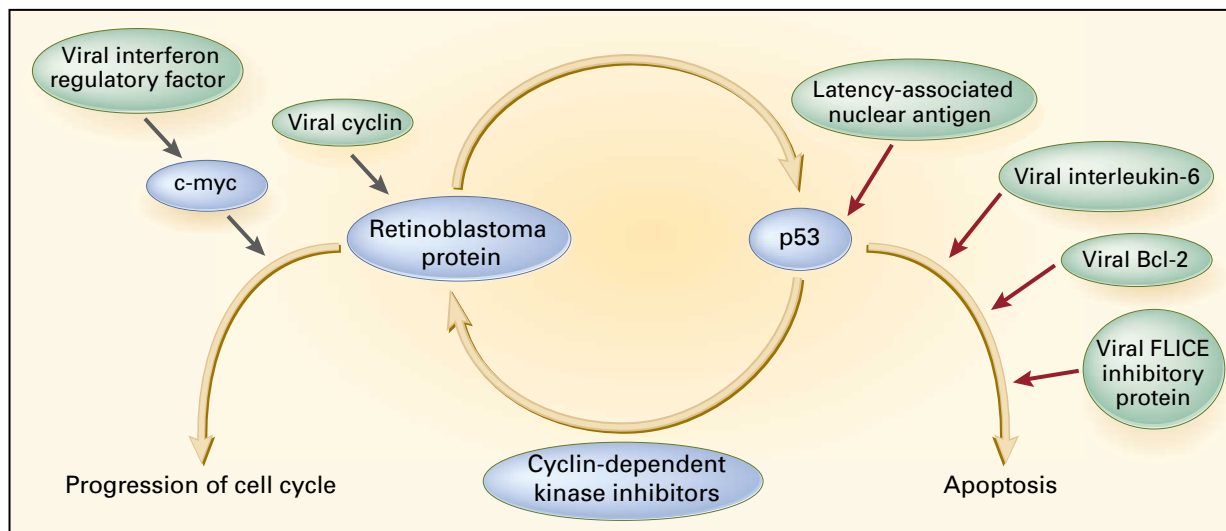


Figure 5. Kaposi's Sarcoma–Associated Herpesvirus Proteins That Interact with the Tumor-Suppressor Pathways Governed by Retinoblastoma Protein and p53.

The viral interferon regulatory factor prevents interferon from repressing c-myc. FLICE denotes Fas-associated death domain–like interleukin-1 β -converting enzyme. Red arrows indicate an inhibitory effect.

or the type of disease. For example, the viral LANA is expressed in all cells infected by KSHV, whereas viral interleukin-6 is only found in KSHV-infected B cells. Localization studies that have used a variety of techniques, from in situ hybridization to immunohistochemical analysis, suggest that although essentially all spindle-shaped cells in a Kaposi's sarcoma lesion are infected by the virus, only a small minority (<1 to 5 percent) contain actively replicating virus.^{39,40} Therefore, some of the potential oncogenes, as defined by in vitro assays of tumorigenicity, are not expressed, and so their contributions to Kaposi's sarcoma in humans remain unclear.

Examination of the larger picture shows that study of KSHV along with other tumor viruses provides important fundamental insights into the way in which cancer cells originate (Fig. 5). Most small DNA tumor viruses (e.g., papillomavirus) have evolved to inhibit two major tumor-suppressor checkpoints in cells: retinoblastoma protein, which controls the cell cycle, and p53, which regulates cellular senescence and apoptosis. Study of KSHV provides evidence that a third pathway can also be inhibited by some tumor viruses.⁴¹ The KSHV viral interferon regulatory factor, as well as oncoproteins from other tumor viruses, prevents interferon from repressing the *c-myc* oncogene.

EPIDEMIOLOGY OF KAPOSI'S SARCOMA AND KSHV

KSHV Infection in Humans

KSHV DNA can be detected in peripheral-blood cells from only about half of infected persons with the use of standard polymerase-chain-reaction (PCR) as-

says, indicating that viremia is not prominent.^{42,43} However, this technique as well as the less sensitive Southern blot hybridization assay can detect viral DNA in virtually all lesions of Kaposi's sarcoma. The identification of a small percentage of lesions as negative for KSHV almost always results from misdiagnosis or suboptimal preparation of specimens. KSHV is clearly associated with Kaposi's sarcoma, body-cavity–related B-cell lymphoma (primary effusion lymphoma), and some plasma-cell forms of multicentric Castlemann's disease. Reports of the involvement of KSHV in other diseases, such as multiple myeloma, sarcoidosis, and post-transplantation skin tumors, have not been confirmed.

Serologic assays to detect KSHV–specific antibodies have high sensitivity, and such methods are preferable to PCR, particularly for detecting previous exposure to the virus. Antibody responses to KSHV antigens appear to be lifelong in most persons, but they may be lost in patients at the end stage of AIDS. The results of serologic studies support the notion that infection with KSHV is nearly universal in patients with Kaposi's sarcoma, since specific antibodies are detectable in 70 to 90 percent of all patients with Kaposi's sarcoma and almost 100 percent of immunocompetent patients with the disease.^{44–48} The results of an indirect immunofluorescence assay for LANA and of an enzyme-linked immunosorbent assay that uses recombinant antigens made from KSHV open-reading-frame (ORF) proteins 65 and K8.1A are highly concordant. When properly performed in standardized formats, these assays can be used in combination for diagnostic purposes.

Rates of Infection in Various Populations

Results of serologic studies show that, unlike other human herpesviruses, KSHV is not ubiquitous. The infection rates instead parallel the incidence of Kaposi's sarcoma, with low rates in the United States, many parts of Europe, and Asia; intermediate rates in Mediterranean countries; and the highest rates in Central Africa (Uganda, Zambia, and South Africa). The seroprevalence of KSHV among blood donors ranges from 0.2 percent in Japan, where Kaposi's sarcoma is rare,⁴⁹ to up to 10 percent in the United States, and to more than 50 percent in many African populations,^{46,47,50-52} with rates in Italy^{50,53} and other Mediterranean countries^{16,46} falling between these extremes. Within this range, there are at-risk populations with particularly high seroprevalence rates. Regardless of their HIV serostatus, homosexual men have a higher rate of Kaposi's sarcoma than the general male population and can have rates of asymptomatic infection that approach 40 percent.^{44,50,54}

Transmission

KSHV can be transmitted sexually and by other means. Sexual transmission predominates in developed countries with a low prevalence of the virus, and it is thought to be more readily transmissible through homosexual than through heterosexual activities. The prevalence of KSHV infection increases with the number of male sexual partners,⁵⁴ and receptive anal intercourse has been identified as a risk factor for infection in some studies.²⁸ In contrast, other modes of transmission predominate in African countries, where infection can occur during childhood.^{51,52} Maternal-infant transmission, whether during labor and delivery or transplacentally, accounts for a portion of KSHV infections in areas where infection is highly endemic.⁵⁵ However, KSHV infection also occurs later in childhood and during adolescence in such areas,⁵⁵ a point that suggests transmission of the virus through some form of nonsexual contact. The exact routes of transmission are not known, although KSHV has been detected in both saliva and semen from infected persons.^{56,57}

Kaposi's sarcoma develops in 0.1 to 1 percent of transplant recipients in areas with a low prevalence of the disease^{8,9} and in up to 5 percent of such patients in areas with a high prevalence.^{14,16} Clinical disease results predominantly from reactivation of the virus, but it may also represent a primary infection transmitted by the transplanted organs.^{15,58} Regamey and colleagues analyzed serum samples from 220 transplant recipients for antibodies against KSHV on the day of transplantation and one year later.⁵⁸ Seroprevalence occurred in 25 patients within the first year after transplantation, and Kaposi's sarcoma developed in 2 of these patients within 26 months after transplantation.⁵⁸ In contrast to the established risk of infection posed by organ transplantation, the

risk of transmission of KSHV through blood products is unknown, although it is clearly lower than that for HIV.

Natural History of KSHV Infection

Most primary KSHV infections appear to be asymptomatic. Clinical and epidemiologic studies have shown that, in healthy adults, there is immunologic control of KSHV infection. In HIV-seropositive patients, the incubation period for diseases caused by KSHV infection largely depends on the host's immune status rather than on the duration of KSHV infection. In some patients with AIDS who are infected with KSHV, the ability of HLA class I-restricted cytotoxic T lymphocytes to respond to KSHV proteins is lost as immunodeficiency worsens and Kaposi's sarcoma develops.⁵⁹ Underscoring the importance of the immune status of the host is the finding that both Kaposi's sarcoma and body-cavity-related B-cell lymphoma have dramatically responded to highly active antiretroviral therapy in patients with AIDS.⁶⁰ Post-transplantation Kaposi's sarcoma has also resolved when immunosuppressive regimens were discontinued.⁸⁻¹⁴

TREATMENT

Classic Kaposi's Sarcoma

Treatments were developed for the classic form of Kaposi's sarcoma, and descriptions of such treatments have chiefly appeared in reports of small studies at single institutions or in case reports. Typically, the disease is multifocal and recurs despite treatment. In one series of 129 patients, only 30 percent were disease-free at 10 years, but only 1 had died of Kaposi's sarcoma.⁶¹

For patients with single lesions, excisional biopsy often provides adequate treatment. Simple excision is also appropriate for resectable recurrences. Of 52 patients who underwent surgery as the primary treatment, 29 (56 percent) had no recurrences for 1 to 162 months (median, 15).⁶¹

Once the diagnosis is established, observation is appropriate for immunocompetent asymptomatic patients with little progression of disease over a long period. Of 39 such patients, 15 (38 percent) remained progression-free for 1 to 83 months (median, 4).⁶¹ In a multivariate analysis, immunosuppression was the only statistically significant independent factor affecting time to progression. Occasionally the disease regresses spontaneously and may not recur for long periods.

Radiation Therapy

Patients with a few lesions in a limited area are often best treated with single doses of radiation (8 to 12 Gy) delivered to an extended field. Symptomatic relief was reported in 95 percent of the patients in one study,⁶¹ and the tumors shrank by at least half

in 74 patients (85 percent), including 50 (58 percent) who had a complete response. Of 60 patients with Kaposi's sarcoma who were treated with radiation therapy in another study, 40 (67 percent) had cutaneous lesions extending above the knees and 8 (13 percent) also had mucous-membrane involvement.⁶² Twenty-one patients were treated with megavoltage electrons. This approach is often ideal because of its limited depth of penetration. Twelve were treated with supervoltage photons, and 27 received both on the basis of the extent, distribution, and depth of the cutaneous lesions. Eleven patients also received whole-body-surface electron irradiation. The overall rate of response was 93 percent after a single fractionated course of radiation therapy. A single dose of 8 to 12 Gy or its equivalent was required to control local cutaneous lesions. Of 25 patients with complete regression of lesions, 18 remained in remission for 2 to 13 years. Widespread visceral involvement was the most common cause of treatment failure and death.

Of 20 patients with Kaposi's sarcoma who received 4 Gy of total-skin electron-beam therapy once a week for 6 to 8 consecutive weeks, 17 (85 percent) had complete remissions, which lasted 10 to 92 months (median, 48).⁶³ All patients had at least some response.

Systemic or Combination Therapy

Patients with extensive or recurrent Kaposi's sarcoma can be treated with a combination of surgery, chemotherapy, and radiation or with chemotherapy alone. Complete remission of disseminated disease can occur after chemotherapy alone or with radiation therapy and can last for several years. Responses can be reliably obtained with vinblastine,^{61,64} bleomycin, doxorubicin, and dacarbazine alone or in combination. In a randomized trial, patients treated with oral etoposide had a higher rate of response than those treated with vinblastine (74 percent vs. 58 percent), and they had less myelosuppression.⁶⁵ (In trials of chemotherapy, a response is defined as a 50 percent decrease in the sum of the perpendicular diameters of each measurable tumor and the appearance of no new lesions for at least one month. The response rate is the percentage of patients whose lesions respond.)

In one study, intralesional injection of interferon alfa-2b at a dose of 1 million to 3 million U resulted in the disappearance of all three lesions so treated as well as in other, uninjected lesions in one patient, and the patient remained in complete remission nine months later.⁶⁶ Intralesional therapy is convenient and has no systemic toxicity, thus providing an attractive alternative to radiation therapy or systemic chemotherapy.⁶⁶ Subcutaneous interferon alfa is also effective, but it has systemic side effects.⁶⁷ In a study of 11 patients who received 3 million U of interferon alfa subcutaneously five times per week, 9 patients had a response, and the response was sustained for 4 to 72 months.⁶⁷

Another study evaluated the effect of hyperthermic perfusion (40°C) of the affected limb with tumor necrosis factor α and melphalan for a period of 90 minutes in five patients.⁶⁸ All five patients had a response.

Endemic Kaposi's Sarcoma

Drugs used to treat classic Kaposi's sarcoma have also proved effective for endemic Kaposi's sarcoma in the few series published. Of 10 Zambian men (mean age, 41 years) who presented with typical endemic Kaposi's sarcoma, all had a prompt response to a combination of dactinomycin and vincristine.⁴ Of 47 HIV-negative South African patients who were treated between 1980 and 1990, the objective rate of response was more than 80 percent with either radiation therapy (29 patients) or chemotherapy (17 patients) (1 patient was not treated).⁵

Immunosuppression-Associated Kaposi's Sarcoma

Kaposi's sarcoma regresses with the cessation, reduction, or modification of immunosuppressive therapy in most patients. A withdrawal or reduction of such therapy in renal-transplant recipients leads to the loss of the graft in approximately half of patients. The discontinuation of immunosuppressive therapy led to the resolution of Kaposi's sarcoma in four of five renal-transplant recipients in a South African study.¹¹ In an Italian study, the withdrawal or reduction of immunosuppressive therapy (plus radiation therapy and chemotherapy in 2 patients) in 13 renal-transplant recipients with Kaposi's sarcoma (5 with skin lesions only and 8 with skin and mucosal or visceral lesions) resulted in complete responses in 9 patients and partial responses in 2, although 4 patients also lost their transplant.¹³ However, in another Italian series, only 4 of 10 renal-transplant recipients with Kaposi's sarcoma had a complete response to a reduction in immunosuppressive therapy.¹⁴ Discontinuation of immunosuppressive therapy is an option in renal-transplant recipients since dialysis is available, but the dose of such drugs can only be reduced or treatment modified in the case of recipients of heart or liver transplants.

The drugs used for classic Kaposi's sarcoma can also be effective for immunosuppression-associated Kaposi's sarcoma. In a Canadian study, five patients who had had no response to a reduction or discontinuation of immunosuppressive therapy or local radiation therapy received a combination of doxorubicin, bleomycin, and vincristine.⁸ Two patients had complete responses, and two had partial responses. The median duration of response was more than 13 months (range, 8 to 45).

Epidemic Kaposi's Sarcoma

The current approach to the management of newly diagnosed Kaposi's sarcoma as the initial manifesta-

tion of AIDS involves the drawing up of a treatment plan by a team experienced in treating patients with AIDS and associated Kaposi's sarcoma. Such patients are usually treated with highly active antiretroviral therapy, with or without treatment directed against Kaposi's sarcoma. The resolution of immunosuppression as a result of highly active antiretroviral therapy may also affect Kaposi's sarcoma.^{69,70} In one study of 13 patients with AIDS and Kaposi's sarcoma who were given highly active antiretroviral therapy, none had progression of Kaposi's sarcoma lesions after a median of 10 weeks (range, 0 to 41) of follow-up.⁷¹ Another study of eight patients reported shrinkage of Kaposi's sarcoma lesions and a decline in KSHV viral loads with highly active antiretroviral therapy.⁷² In other case reports, Kaposi's sarcoma responded concurrently with the decrease of the serum level of HIV RNA and the increase in the CD4 count.^{60,71} In a group of patients with Kaposi's sarcoma who were receiving either foscarnet or ganciclovir — both of which are effective against cytomegalovirus infection — those receiving foscarnet had a significantly longer interval before the progression of Kaposi's sarcoma than those receiving ganciclovir.⁷² However, because the response of Kaposi's sarcoma to highly active antiretroviral therapy is unpredictable, specific local or systemic therapy is often instituted as well.

Radiation Therapy

Although epidemic Kaposi's sarcoma responds to radiation therapy and chemotherapy, the response is less durable than in classic Kaposi's sarcoma. HIV-positive patients with Kaposi's sarcoma lesions involving limited areas of the skin or oral mucosa are often most easily treated with radiation. In one randomized study, higher total doses of fractionated radiation therapy significantly improved the control of cutaneous Kaposi's sarcoma, as compared with lower total doses.⁷³

Cytotoxic Drugs

Patients with Kaposi's sarcoma who have widespread mucocutaneous disease, lymphedema, or visceral disease are usually treated with systemic cytotoxic therapy. The most active drugs include liposomal anthracyclines, paclitaxel, vinca alkaloids, and bleomycin. The cytotoxic drugs with activity against classic Kaposi's sarcoma are also active against epidemic Kaposi's sarcoma but are generally associated with lower response rates and shorter responses. Studies have reported rates of partial response of 26 percent (10 of 38 patients) for weekly vinblastine,⁷⁴ 10 to 48 percent for doxorubicin,^{75,76} and 36 percent for weekly doses of oral etoposide.⁷⁷ The combination of doxorubicin, bleomycin, and vinblastine was well tolerated and resulted in rates of partial and complete response of 88 percent,⁷⁵ but it has largely been replaced by newer drugs and combinations.

Liposomal anthracyclines are effective against Kaposi's sarcoma and may be less toxic than nonliposomal anthracyclines. Liposomal daunorubicin given intravenously every two weeks produced response rates of 25 to 62 percent.⁷⁸⁻⁸¹ In a randomized comparison of liposomal daunorubicin every two weeks with a combination of doxorubicin, bleomycin, and vincristine, each given every two weeks, the response rates were similar (25 percent vs. 28 percent).⁸¹ However, in a randomized comparison of polyethylene glycol (PEG)-conjugated liposomal doxorubicin (every three weeks) with a combination of bleomycin (every three weeks) and vincristine (every three weeks), the doxorubicin therapy was associated with a significantly higher response rate (59 percent vs. 23 percent).⁸²

Another study reported similar results when treatment consisted of PEG-conjugated liposomal doxorubicin (every two weeks) or a combination of doxorubicin, bleomycin, and vincristine (each given every two weeks).⁸³ Again, the single drug was associated with a significantly higher rate of response (46 percent vs. 25 percent) and was also less neurotoxic than combination therapy. On the basis of these studies, liposomal doxorubicin, although more myelosuppressive than the combination of bleomycin and vincristine, is now considered by many physicians the first-line therapy for patients with advanced Kaposi's sarcoma.

Paclitaxel, a drug that stabilizes microtubules, also has antiangiogenic effects.⁸⁴ In three studies of a total of 105 patients who were treated with paclitaxel, response rates ranged from 49 percent to 71 percent.⁸⁵⁻⁸⁷ Thus, paclitaxel is an excellent second-line therapy.

Biologic Agents

Biologic agents such as interferon alfa are now considered first-line therapy for some patients with epidemic cutaneous Kaposi's sarcoma. Subcutaneous, intravenous, or intralesional interferon alfa all resulted in remissions in 20 to 60 percent of patients studied⁸⁸⁻⁹² — results that are similar to those for single-agent chemotherapy. Response rates correlate with base-line CD4 counts and the use of antiviral therapy. The low rates of opportunistic infection in patients with a response may be attributable to a higher base-line level of immunocompetence, immune enhancement,⁹³ or even a direct antiviral effect.⁹² When given as a single agent, interferon alfa at a dose of 30 million U per day intravenously or intramuscularly provides the best results. In one randomized study, an intravenous dose of 50 million U was compared with a subcutaneous dose of 1 million U, both given five days per week every other week, with response rates of 40 percent and 20 percent, respectively.⁸⁸ Daily dosing regimens may minimize the common side effects of fever, chills, fatigue, and muscle pain. Responses are least likely in patients with recent serious

infections, fever and weight loss, and high base-line levels of circulating acid-labile interferon- α ,⁹³ and the likelihood of a response is correlated with CD4 counts.⁹²

Interferon in Combination with Antiretroviral Therapy

In 1991, de Wit et al. reported the feasibility of combining interferon alfa and zidovudine in patients with Kaposi's sarcoma.⁹⁰ An AIDS Clinical Trials Group study of subcutaneous interferon alfa and zidovudine concluded that because of constitutional symptoms in these patients, the maximal dose of interferon was 10 million U subcutaneously per day.⁹⁴ Two subsequent randomized trials studied the efficacy of concurrent treatment with zidovudine (500 mg daily) and interferon alfa. In the first, zidovudine and interferon alfa (1 million U subcutaneously per day) was compared with interferon alfa alone (8 million U subcutaneously per day). The rate of response was significantly higher in the group given combination therapy (31 percent vs. 8 percent), and the median time to tumor progression was significantly longer (18 weeks vs. 13 weeks).⁹⁵ In the second study, zidovudine and interferon alfa (9 million U subcutaneously per day) were compared with bleomycin alone (every two weeks). The incidence of side effects was similar in the two groups. Although the response rate was higher in the bleomycin group (20 percent vs. 8 percent), median survival was longer in the combination-therapy group (24 months vs. 13 months).⁹⁶

Experimental Therapies

Inhibitors of angiogenesis, such as an inhibitor of vascular endothelial growth factor and thalidomide,^{97,98} and retinoids (differentiating agents), such as all-*trans*-retinoic acid (tretinoin) and oral 9-*cis*-retinoic acid (LGD 1057),⁹⁹ have activity against Kaposi's sarcoma. In one patient given thalidomide, Kaposi's sarcoma lesions regressed and levels of KSHV DNA were no longer detectable in blood and were reduced in the tumor.⁹⁸ In a study of 17 patients who were given 100 mg of thalidomide orally once nightly for eight weeks, the response rate was 35 percent. The KSHV DNA titer decreased at least 3 log and was undetectable in three of five patients with a response.⁹⁷

In laboratory models of Kaposi's sarcoma, treatment with retinoic acid blocked the proliferative effect of oncostatin M and tumor necrosis factor α , two major autocrine growth factors in Kaposi's sarcoma, and increased nuclear staining for retinoic acid receptor α and the relative number of nuclei that were strongly positive for this receptor.¹⁰⁰ Kaposi's sarcoma cells became more flattened and spread out and more adhesive to the substrate. In another study, retinoic acid and its synthetic analogues inhibited the proliferation of Kaposi's sarcoma cells by inhibiting viral messenger RNA and levels of interleukin-6, an autocrine growth factor.¹⁰¹

In an American study, 27 patients with mucocutaneous, nonvisceral AIDS-related Kaposi's sarcoma were treated with all-*trans*-retinoic acid daily. Four of 24 patients who could be evaluated (17 percent) had a partial response after 12 to 28 weeks of therapy, and the response lasted for 4 to 24 weeks.¹⁰² In a French study of 20 patients, 42 percent had a response to treatment with all-*trans*-retinoic acid (orally every day for 12 weeks), and the response lasted for a median of 11 months.⁹⁹ However, of 15 men with high-risk Kaposi's sarcoma who were treated with oral 13-*cis*-retinoic acid, only 1 patient (7 percent) had a partial response.¹⁰³ Early results of studies of oral 9-*cis*-retinoic acid also suggest that it is active against Kaposi's sarcoma.

In a laboratory model, human chorionic gonadotropin killed cells from two Kaposi's sarcoma cell lines (apparently by apoptosis) as well as cells from clinical specimens grown in short-term culture.¹⁰⁴ Although commercially available preparations of β -human chorionic gonadotropin have variable effects, purified human chorionic gonadotropin had little activity, suggesting that the active component may be a contaminant.^{105,106} A subsequent clinical study showed that lesions injected with human chorionic gonadotropin resolved but that those injected with diluent did not.¹⁰⁵

PREVENTION

Given that candidates for organ transplantation and HIV-positive patients who are seropositive for KSHV and thus at risk for Kaposi's sarcoma can now be identified, chemoprevention should be possible in these two high-risk populations. Such strategies in KSHV-seropositive candidates for organ transplantation should be directed against the virus itself, and the immunosuppressive regimen should be carefully monitored to avoid the possibility of rejection. In patients with AIDS, strategies directed against HIV, Kaposi's sarcoma, or both viruses could prove effective. Resolution of immunosuppression as a result of highly active antiretroviral therapy may also prevent Kaposi's sarcoma.

Laboratory studies of the susceptibility of KSHV to antiviral drugs suggest that the virus is resistant to acyclovir and penciclovir but sensitive to ganciclovir, foscarnet, and cidofovir.¹⁰⁷ In one study, acyclovir and penciclovir had weak-to-moderate activity against KSHV, whereas ganciclovir had pronounced activity.¹⁰⁸ Cidofovir potentially inhibited the synthesis of KSHV DNA, and the concentration of adefovir required to block the replication of KSHV DNA was lower than that of foscarnet.¹⁰⁸

In clinical studies of cytomegalovirus end-organ disease in patients with Kaposi's sarcoma who received either ganciclovir (20 patients) or foscarnet (46 patients) for at least 14 days, the median time to progression of Kaposi's sarcoma was 211 days in the foscarnet group and 22 days in the ganciclovir group

($P < 0.001$).⁷² A history of visceral Kaposi's sarcoma or previous treatment with ganciclovir significantly increased the risk of progression. In a study of patients with AIDS and cytomegalovirus retinitis, patients were randomly assigned to receive a ganciclovir implant plus oral ganciclovir (4.5 g daily), a ganciclovir implant plus oral placebo, or intravenous ganciclovir alone.¹⁰⁹ As compared with placebo, oral ganciclovir reduced the risk of Kaposi's sarcoma by 75 percent ($P = 0.008$) and intravenous ganciclovir reduced the risk by 93 percent ($P < 0.001$).

In a study of HIV-infected patients who were either monitored or treated with 3 million U of interferon alfa-2b three times per week, there was one case of Kaposi's sarcoma among those receiving interferon alfa-2b, as compared with five in the observation group.¹¹⁰ Other studies of interferon have not shown that the drug has a protective effect, and zidovudine has also not been shown to have an antitumor effect.^{111,112}

All the drugs studied so far have clinically significant systemic side effects and are generally unsuitable for long-term prophylactic use. Other drugs with fewer side effects and greater ease of administration might, however, prove effective in preventing Kaposi's sarcoma in persons at risk.

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