

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

KAREN ANTMAN, M.D., AND YUAN CHANG, M.D.

**I**N 1872, Moritz Kaposi, a Hungarian dermatologist, described five men with aggressive "idiopathic multiple pigmented sarcomas of the skin."<sup>1</sup> 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).<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup> Four of the 47 had concurrent lymphoma.<sup>5</sup> Typical findings in 10 Zambian men (median age, 41 years) with indolent disease were nodules or plaques on edematous limbs.<sup>4</sup> 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.<sup>6</sup> An aggressive lymphadenopathic Kaposi's sarcoma affects African children in particular.<sup>7</sup> 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.<sup>7</sup>

**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.<sup>8-17</sup> In a series of 2099 organ-transplant

From the Departments of Medicine (K.A.) and Pathology (Y.C.), Columbia University College of Physicians and Surgeons, New York. Address reprint requests to Dr. Chang at P&S14-442, Department of Pathology, Columbia University College of Physicians and Surgeons, 630 W. 168th St., New York, NY 10032.

©2000, Massachusetts Medical Society.

**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  |

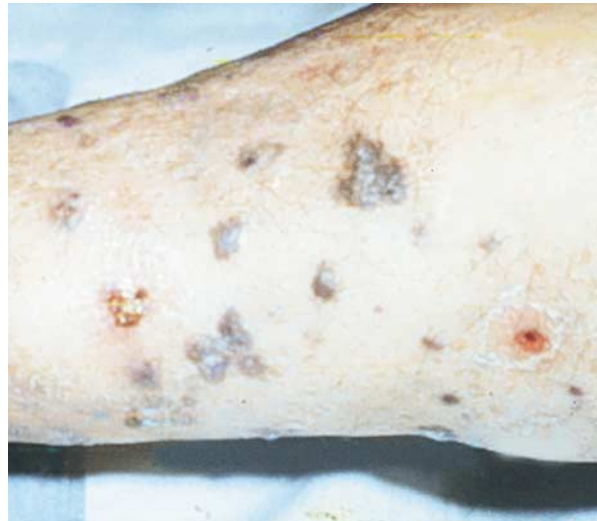
\*AIDS denotes acquired immunodeficiency syndrome.

recipients studied at the Toronto Hospital, Kaposi's sarcoma developed in 12 (0.6 percent), 9 of whom were of Italian origin.<sup>8</sup> The Collaborative Transplantation Research Group of Ile de France<sup>9</sup> 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.<sup>17</sup>

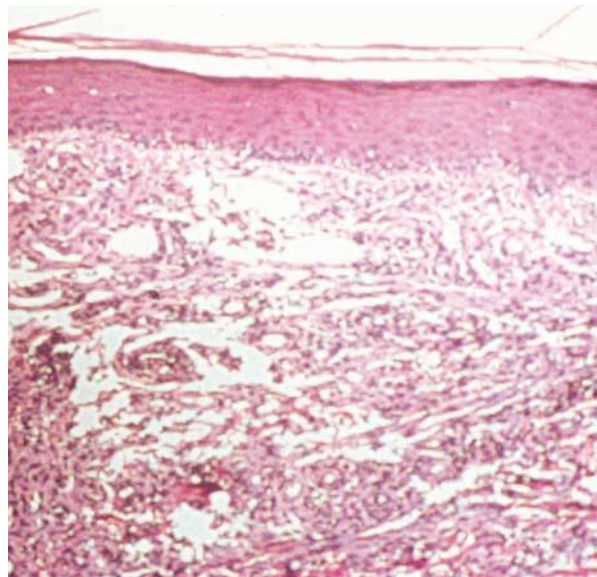
The median interval from organ transplantation to the diagnosis of Kaposi's sarcoma is 29 to 31 months (range, 3 to 124 months).<sup>13,14</sup> In three series with a total of 35 cases of Kaposi's sarcoma, the percentage of men in whom Kaposi's sarcoma developed ranged from 67 percent to 80 percent, with a ratio of male to female patients ranging from 2:1 to 4:1.<sup>8,13,14</sup> 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.<sup>18-20</sup>

#### 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.<sup>21</sup> 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.<sup>22</sup> 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,<sup>23</sup> it remains the most common AIDS-associated cancer in the United States.



A



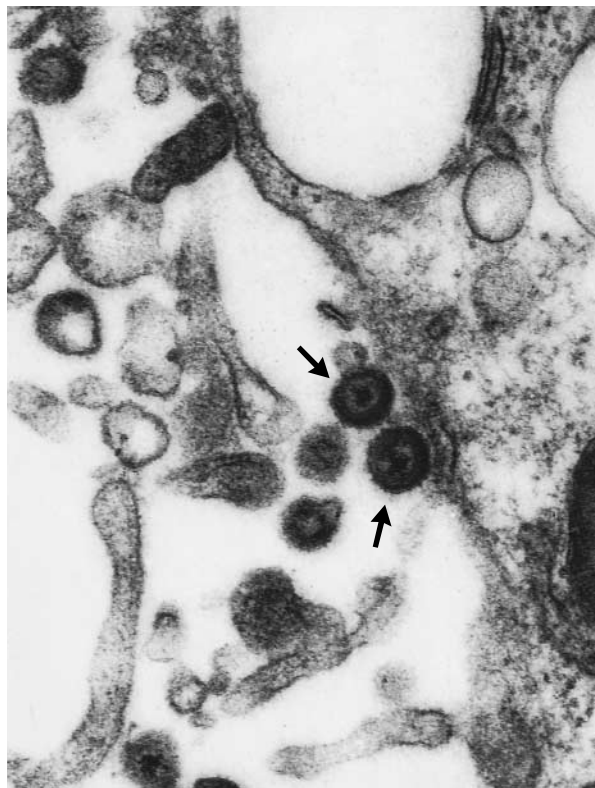
B

**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.<sup>22</sup> 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.)

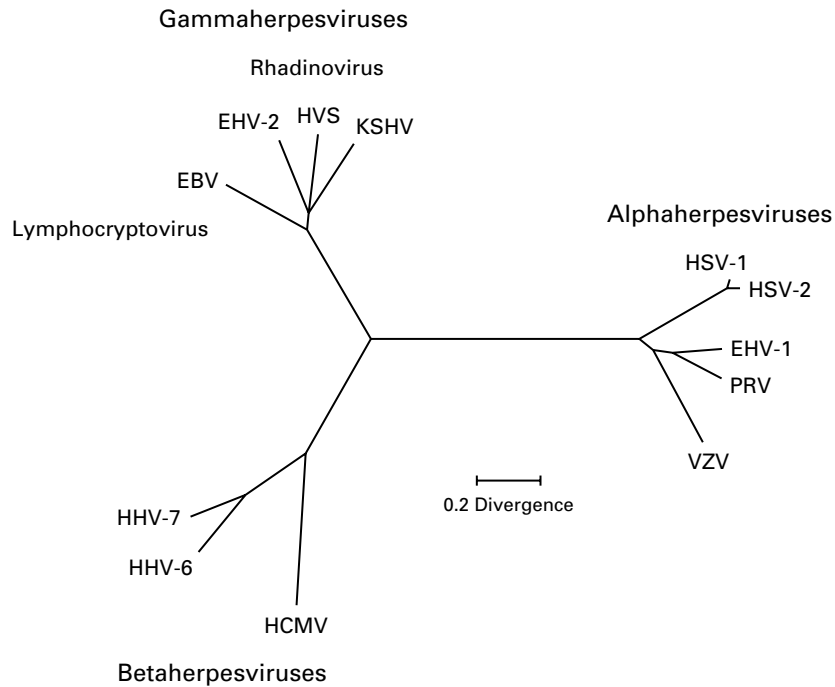
been called Kaposi's sarcoma–associated herpesvirus (KSHV, also known as human herpesvirus 8), in a Kaposi's sarcoma skin lesion from a patient with AIDS.<sup>24</sup> Over 95 percent of Kaposi's sarcoma lesions, regardless of their source or clinical subtype, have been found to be infected with KSHV (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.<sup>25</sup> 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.<sup>26</sup> 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.<sup>27,28</sup> 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.<sup>28</sup>

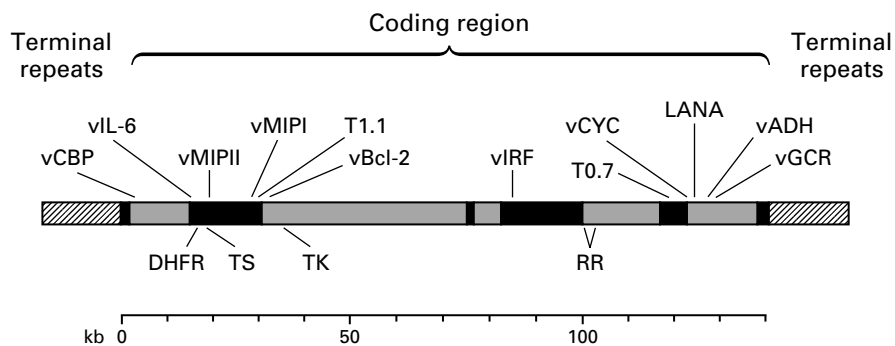
The 165-kb KSHV genome was sequenced within two years after its discovery,<sup>29</sup> which provided important clues about the way in which this virus might induce uncontrolled cellular proliferation. Unlike most other viruses, KSHV incorporated several recognizable host-cell genes during its evolution (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,<sup>30</sup> and a Bcl-2–like protein that prevents apoptosis.<sup>31</sup> Other regulatory KSHV proteins include a G-protein–coupled receptor,<sup>32</sup> an inhibitor of apoptosis mediated by the FLICE (Fas-associated death domain–like interleukin-1 $\beta$ –converting enzyme) pathway,<sup>33</sup> a constitutively active immunoreceptor,<sup>34</sup> and an inhibitor of the interferon signaling pathway,<sup>35</sup> 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.<sup>36</sup> 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.<sup>37</sup> Recently, Friberg et al. demonstrated that the major latency-associated nuclear antigen (LANA) can interact with p53 and inhibit transcriptional activity mediated by p53.<sup>38</sup>

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



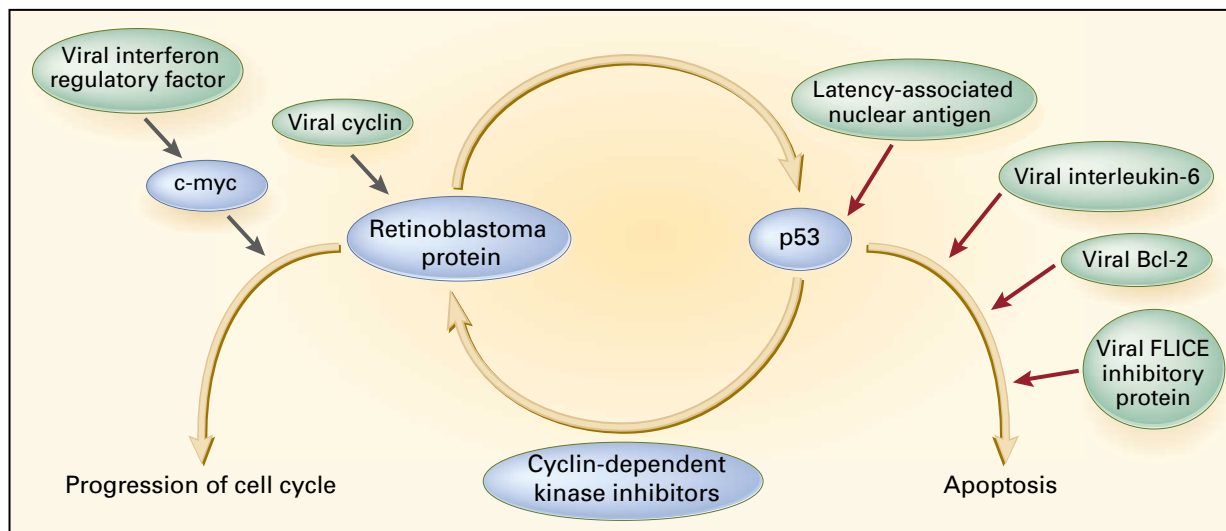
**Figure 3.** Phylogenetic Tree of Known Human Herpesviruses as Well as Several Other Herpesviruses That Have Nonhuman Hosts.

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.<sup>25</sup> 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 (vMIP1) and type II (vMIP2), 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 $\beta$ -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.<sup>39,40</sup> 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.<sup>41</sup> 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.<sup>42,43</sup> 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.<sup>44–48</sup> 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,<sup>49</sup> to up to 10 percent in the United States, and to more than 50 percent in many African populations,<sup>46,47,50-52</sup> with rates in Italy<sup>50,53</sup> and other Mediterranean countries<sup>16,46</sup> 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.<sup>44,50,54</sup>

### 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,<sup>54</sup> and receptive anal intercourse has been identified as a risk factor for infection in some studies.<sup>28</sup> In contrast, other modes of transmission predominate in African countries, where infection can occur during childhood.<sup>51,52</sup> Maternal-infant transmission, whether during labor and delivery or transplacentally, accounts for a portion of KSHV infections in areas where infection is highly endemic.<sup>55</sup> However, KSHV infection also occurs later in childhood and during adolescence in such areas,<sup>55</sup> 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.<sup>56,57</sup>

Kaposi's sarcoma develops in 0.1 to 1 percent of transplant recipients in areas with a low prevalence of the disease<sup>8,9</sup> and in up to 5 percent of such patients in areas with a high prevalence.<sup>14,16</sup> Clinical disease results predominantly from reactivation of the virus, but it may also represent a primary infection transmitted by the transplanted organs.<sup>15,58</sup> Regamey and colleagues analyzed serum samples from 220 transplant recipients for antibodies against KSHV on the day of transplantation and one year later.<sup>58</sup> 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.<sup>58</sup> 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.<sup>59</sup> 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.<sup>60</sup> Post-transplantation Kaposi's sarcoma has also resolved when immunosuppressive regimens were discontinued.<sup>8-14</sup>

## 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.<sup>61</sup>

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).<sup>61</sup>

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).<sup>61</sup> 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,<sup>61</sup> 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.<sup>62</sup> 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).<sup>63</sup> 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,<sup>61,64</sup> 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.<sup>65</sup> (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.<sup>66</sup> Intralesional therapy is convenient and has no systemic toxicity, thus providing an attractive alternative to radiation therapy or systemic chemotherapy.<sup>66</sup> Subcutaneous interferon alfa is also effective, but it has systemic side effects.<sup>67</sup> 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.<sup>67</sup>

Another study evaluated the effect of hyperthermic perfusion (40°C) of the affected limb with tumor necrosis factor  $\alpha$  and melphalan for a period of 90 minutes in five patients.<sup>68</sup> 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.<sup>4</sup> 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).<sup>5</sup>

#### **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.<sup>11</sup> 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.<sup>13</sup> 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.<sup>14</sup> 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.<sup>8</sup> 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.<sup>69,70</sup> 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.<sup>71</sup> Another study of eight patients reported shrinkage of Kaposi's sarcoma lesions and a decline in KSHV viral loads with highly active antiretroviral therapy.<sup>72</sup> 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.<sup>60,71</sup> 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.<sup>72</sup> 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.<sup>73</sup>

#### **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,<sup>74</sup> 10 to 48 percent for doxorubicin,<sup>75,76</sup> and 36 percent for weekly doses of oral etoposide.<sup>77</sup> The combination of doxorubicin, bleomycin, and vinblastine was well tolerated and resulted in rates of partial and complete response of 88 percent,<sup>75</sup> 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.<sup>78-81</sup> 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).<sup>81</sup> 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).<sup>82</sup>

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).<sup>83</sup> 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.<sup>84</sup> In three studies of a total of 105 patients who were treated with paclitaxel, response rates ranged from 49 percent to 71 percent.<sup>85-87</sup> 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 studied<sup>88-92</sup> — 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,<sup>93</sup> or even a direct antiviral effect.<sup>92</sup> 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.<sup>88</sup> 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- $\alpha$ ,<sup>93</sup> and the likelihood of a response is correlated with CD4 counts.<sup>92</sup>

#### **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.<sup>90</sup> 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.<sup>94</sup> 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).<sup>95</sup> 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).<sup>96</sup>

#### **Experimental Therapies**

Inhibitors of angiogenesis, such as an inhibitor of vascular endothelial growth factor and thalidomide,<sup>97,98</sup> and retinoids (differentiating agents), such as all-*trans*-retinoic acid (tretinoin) and oral 9-*cis*-retinoic acid (LGD 1057),<sup>99</sup> 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.<sup>98</sup> 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.<sup>97</sup>

In laboratory models of Kaposi's sarcoma, treatment with retinoic acid blocked the proliferative effect of oncostatin M and tumor necrosis factor  $\alpha$ , two major autocrine growth factors in Kaposi's sarcoma, and increased nuclear staining for retinoic acid receptor  $\alpha$  and the relative number of nuclei that were strongly positive for this receptor.<sup>100</sup> 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.<sup>101</sup>

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.<sup>102</sup> 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.<sup>99</sup> 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.<sup>103</sup> 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.<sup>104</sup> Although commercially available preparations of  $\beta$ -human chorionic gonadotropin have variable effects, purified human chorionic gonadotropin had little activity, suggesting that the active component may be a contaminant.<sup>105,106</sup> A subsequent clinical study showed that lesions injected with human chorionic gonadotropin resolved but that those injected with diluent did not.<sup>105</sup>

#### **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.<sup>107</sup> In one study, acyclovir and penciclovir had weak-to-moderate activity against KSHV, whereas ganciclovir had pronounced activity.<sup>108</sup> 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.<sup>108</sup>

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

( $P < 0.001$ ).<sup>72</sup> 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.<sup>109</sup> 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.<sup>110</sup> 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.<sup>111,112</sup>

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.

Supported in part by grants (P20CA66244-01 and CA167391) from the National Cancer Institute.

*We are indebted to Patrick S. Moore, M.D., M.P.H., Scott Hammer, M.D., and Mary L. Keohan, M.D., for review of and comments on the manuscript.*

## REFERENCES

- Kaposi M. Idiopathic multiple pigmented sarcoma of the skin. *CA Cancer J Clin* 1982;32:342-7.
- DiGiovanna JJ, Safai B. Kaposi's sarcoma: retrospective study of 90 cases with particular emphasis on the familial occurrences, ethnic background and prevalence of other diseases. *Am J Med* 1981;71:779-83.
- Taylor JF, Templeton AC, Vogel CL, Ziegler JL, Kyalwazi SK. Kaposi's sarcoma in Uganda: a clinico-pathological study. *Int J Cancer* 1971;8:122-35.
- Bayley AC. Aggressive Kaposi's sarcoma in Zambia, 1983. *Lancet* 1984;1:1318-20.
- Stein ME, Spencer D, Ruff P, Lakier R, MacPhail P, Bezwoda WR. Endemic African Kaposi's sarcoma: clinical and therapeutic implications: 10-year experience in the Johannesburg Hospital (1980-1990). *Oncology* 1994;51:63-9.
- Wabinga HR, Parkin DM, Wabwire-Mangen F, Mugerwa JW. Cancer in Kampala, Uganda, in 1989-91: changes in incidence in the era of AIDS. *Int J Cancer* 1993;54:26-36.
- Athale UH, Patil PS, Chintu C, Elem B. Influence of HIV epidemic on the incidence of Kaposi's sarcoma in Zambian children. *J Acquir Immune Defic Syndr Hum Retroviro* 1995;8:96-100.
- Shepherd FA, Maher E, Cardella C, et al. Treatment of Kaposi's sarcoma after solid organ transplantation. *J Clin Oncol* 1997;15:2371-7.
- Farge D. Kaposi's sarcoma in organ transplant recipients. *Eur J Med* 1993;2:339-43.
- Farge D, Lebbe C, Marjanovic Z, et al. Human herpes virus-8 and other risk factors for Kaposi's sarcoma in kidney transplant recipients. *Transplantation* 1999;67:1236-42.
- Margolius L, Stein M, Spencer D, Bezwoda WR. Kaposi's sarcoma in renal transplant recipients: experience at Johannesburg Hospital, 1966-1989. *S Afr Med J* 1994;84:16-7.
- Szende B, Toth A, Perner F, Nagy K, Takacs K. Clinicopathological aspects of 8 Kaposi's sarcomas among 1009 renal transplant patients. *Gen Diagn Pathol* 1997;143:209-13.
- Montagnino G, Bencini PL, Tarantino A, Caputo R, Ponticelli C. Clinical features and course of Kaposi's sarcoma in kidney transplant patients: report of 13 cases. *Am J Nephrol* 1994;14:121-6.
- Lesnoni La Parola I, Masini C, Nanni G, Diociaiuti A, Panocchia N, Cerimele D. Kaposi's sarcoma in renal-transplant recipients: experience at the Catholic University in Rome, 1988-1996. *Dermatology* 1997;194:229-33.
- Parravicini C, Olsen SJ, Capra M, et al. Risk of Kaposi's sarcoma-associated herpes virus transmission from donor allografts among Italian posttransplant Kaposi's sarcoma patients. *Blood* 1997;90:2826-9.
- Qunibi W, Al-Furayh O, Almehari K, et al. Serologic association of human herpesvirus eight with posttransplant Kaposi's sarcoma in Saudi Arabia. *Transplantation* 1998;65:583-5.
- Qunibi W, Akhtar M, Sheth K, et al. Kaposi's sarcoma: the most common tumor after renal transplantation in Saudi Arabia. *Am J Med* 1988;84:225-32.
- Malekzadeh MH, Church JA, Siegel SE, Mitchell WG, Opas L, Lieberman E. Human immunodeficiency virus-associated Kaposi's sarcoma in a pediatric renal transplant recipient. *Nephron* 1987;47:62-5.
- Strauchen JA, Hauser AD, Burstein D, Jimenez R, Moore PS, Chang Y. Body cavity-based malignant lymphoma containing Kaposi sarcoma-associated herpesvirus in an HIV-negative man with previous Kaposi sarcoma. *Ann Intern Med* 1996;125:822-5.
- Wang AY, Li PK, To KE, Lai FM, Lai KN. Coexistence of Kaposi's sarcoma and tuberculosis in a renal transplant recipient. *Transplantation* 1998;66:115-8.
- Friedman-Kien AE, Laubenstein L, Marmor M, et al. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men — New York City and California. *MMWR Morb Mortal Wkly Rep* 1981;30:305-8.
- Beral V, Peterman TA, Berkelman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? *Lancet* 1990;335:123-8.
- Biggar RJ, Rabkin CS. The epidemiology of AIDS-related neoplasms. *Hematol Oncol Clin North Am* 1996;10:997-1010.
- Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 1994;266:1865-9.
- Moore PS, Gao SJ, Dominguez G, et al. Primary characterization of a herpesvirus agent associated with Kaposi's sarcoma. *J Virol* 1996;70:549-58. [Erratum, *J Virol* 1996;70:9083.]
- Hayward GS. KSHV strains: the origins and global spread of the virus. *Semin Cancer Biol* 1999;9:187-99.
- Archibald CP, Schechter MT, Craib KJ, et al. Risk factors for Kaposi's sarcoma in the Vancouver Lymphadenopathy-AIDS Study. *J AIDS* 1990;3: Suppl 1:S18-S23.
- Melbye M, Cook PM, Hjalgrim H, et al. Risk factors for Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) seropositivity in a cohort of homosexual men, 1981-1996. *Int J Cancer* 1998;77:543-8.
- Russo JJ, Bohenzky RA, Chien MC, et al. Nucleotide sequence of the Kaposi sarcoma-associated herpesvirus (HHV8). *Proc Natl Acad Sci U S A* 1996;93:14862-7.
- Chang Y, Moore PS, Talbot SJ, et al. Cyclin encoded by KS herpesvirus. *Nature* 1996;382:410.
- Cheng EH, Nicholas J, Bellows DS, et al. A Bcl-2 homolog encoded by Kaposi sarcoma-associated virus, human herpesvirus 8, inhibits apoptosis but does not heterodimerize with Bax or Bak. *Proc Natl Acad Sci U S A* 1997;94:690-4.
- Bais C, Santomasso B, Coso O, et al. G-protein-coupled receptor of Kaposi's sarcoma-associated herpesvirus is a viral oncogene and angiogenesis activator. *Nature* 1998;391:86-9. [Erratum, *Nature* 1998;392:210.]
- Thome M, Schneider P, Hofmann K, et al. Viral FLICE-inhibitory proteins (FLIPs) prevent apoptosis induced by death receptors. *Nature* 1997;386:517-21.
- Lee H, Veazey R, Williams K, et al. Deregulation of cell growth by the K1 gene of Kaposi's sarcoma-associated herpesvirus. *Nat Med* 1998;4:435-40.
- Gao S-J, Boshoff C, Jayachandra S, Weiss RA, Chang Y, Moore PS. KSHV ORF K9 (vIRF) is an oncogene which inhibits the interferon signaling pathway. *Oncogene* 1997;15:1979-85.
- Moore PS, Boshoff C, Weiss RA, Chang Y. Molecular mimicry of human cytokine and cytokine response pathway genes by KSHV. *Science* 1997;274:1739-44.
- Stine JT, Wood C, Hill M, et al. KSHV-encoded CC chemokine is a CCR4 agonist, stimulates angiogenesis, and selectively chemoattracts TH2 cells. *Blood* 2000;95:1151-7.
- Friborg J Jr, Kong W, Hottiger MO, Nabel GJ. p53 Inhibition by the LANA protein of KSHV protects against cell death. *Nature* 1999;402:889-94.
- Dupin N, Fisher C, Kellam P, et al. Distribution of human herpesvirus-8 latently infected cells in Kaposi's sarcoma, multicentric Castleman's disease, and primary effusion lymphoma. *Proc Natl Acad Sci U S A* 1999;96:4546-51.

40. Zhong W, Wang H, Herdier B, Gancm D. Restricted expression of Kaposi sarcoma-associated herpesvirus (human herpesvirus 8) genes in Kaposi sarcoma. *Proc Natl Acad Sci U S A* 1996;93:6641-6.
41. Jayachandra S, Low K, Thlick A-E, et al. Three unrelated viral transforming proteins (vIRF, EBNA2, and E1A) induce the MYC oncogene through the interferon responsive PRF element by using different transcription coadaptors. *Proc Natl Acad Sci U S A* 1999;96:11566-71.
42. Whitby D, Howard MR, Tenant-Flowers M, et al. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. *Lancet* 1995;364:799-802.
43. Moore PS, Kingsley LA, Holmberg SD, et al. Kaposi's sarcoma-associated herpesvirus infection prior to onset of Kaposi's sarcoma. *AIDS* 1996;10:175-80.
44. Miller G, Rigby MO, Heston L, et al. Antibodies to butyrate-inducible antigens of Kaposi's sarcoma-associated herpesvirus in patients with HIV-1 infection. *N Engl J Med* 1996;334:1292-7.
45. Gao S-J, Kingsley L, Hoover DR, et al. Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi's sarcoma. *N Engl J Med* 1996;335:233-41.
46. Simpson GR, Schulz TF, Whitby D, et al. Prevalence of Kaposi's sarcoma associated herpesvirus infection measured by antibodies to recombinant capsid protein and latent immunofluorescence antigen. *Lancet* 1996;348:1133-8.
47. Lennette ET, Blackburn DJ, Levy JA. Antibodies to human herpesvirus type 8 in the general population and in Kaposi's sarcoma patients. *Lancet* 1996;348:858-61.
48. Kedes DH, Operskalski E, Busch M, Kohn R, Flood J, Ganem D. The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus): distribution of infection in KS risk groups and evidence for sexual transmission. *Nat Med* 1996;2:918-24. [Erratum, *Nat Med* 1996;2:1041.]
49. Fujii T, Taguchi H, Katano H, et al. Seroprevalence of human herpesvirus 8 in human immunodeficiency virus 1-positive and human immunodeficiency virus 1-negative populations in Japan. *J Med Virol* 1999;57:159-62.
50. Gao SJ, Kingsley L, Li M, et al. KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma. *Nat Med* 1996;2:925-8.
51. Olsen SJ, Chang Y, Moore PS, Biggar RJ, Melbye M. Increasing Kaposi's sarcoma-associated herpesvirus seroprevalence with age in a highly Kaposi's sarcoma endemic region, Zambia in 1985. *AIDS* 1998;12:1921-5.
52. Sitas F, Carrara H, Beral V, et al. Antibodies against human herpesvirus 8 in black South African patients with cancer. *N Engl J Med* 1999;340:1863-71.
53. Whitby D, Luppi M, Barozzi P, Boshoff C, Weiss RA, Torelli G. Human herpesvirus 8 seroprevalence in blood donors and lymphoma patients from different regions of Italy. *J Natl Cancer Inst* 1998;90:395-7.
54. Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes DH. Sexual transmission and the natural history of human herpesvirus 8 infection. *N Engl J Med* 1998;338:948-54.
55. Mayama S, Cuevas LE, Sheldon J, et al. Prevalence and transmission of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) in Ugandan children and adolescents. *Int J Cancer* 1998;77:817-20.
56. Koelle DM, Huang ML, Chandran B, Vieira J, Piepkorn M, Corey L. Frequent detection of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) DNA in saliva of human immunodeficiency virus-infected men: clinical and immunologic correlates. *J Infect Dis* 1997;176:94-102.
57. Pellett PE, Spira TJ, Bagasra O, et al. Multicenter comparison of PCR assays for detection of human herpesvirus 8 DNA in semen. *J Clin Microbiol* 1999;37:1298-301.
58. Regamey N, Tamm M, Wernli M, et al. Transmission of human herpesvirus 8 infection from renal-transplant donors to recipients. *N Engl J Med* 1998;339:1358-63.
59. Osman M, Kubo T, Gill J, et al. Identification of human herpesvirus 8-specific cytotoxic T-cell responses. *J Virol* 1999;73:6136-40.
60. Winceclaus J. Regression of AIDS-related pleural effusion with HAART: highly active antiretroviral therapy. *Int J STD AIDS* 1998;9:368-70.
61. Brenner B, Rakowsky E, Katz A, et al. Tailoring treatment for classical Kaposi's sarcoma: comprehensive clinical guidelines. *Int J Oncol* 1999;14:1097-102.
62. Lo TC, Salzman FA, Smedal MI, Wright KA. Radiotherapy for Kaposi's sarcoma. *Cancer* 1980;45:684-7.
63. Nisce LZ, Safai B, Poussin-Rosillo H. Once weekly total and subtotal skin electron beam therapy for Kaposi's sarcoma. *Cancer* 1981;47:640-4.
64. Klein E, Schwartz RA, Laor Y, Milgrom H, Burgess GH, Holtermann OA. Treatment of Kaposi's sarcoma with vinblastine. *Cancer* 1980;45:427-31.
65. Brambilla L, Labianca R, Boneschi V, et al. Mediterranean Kaposi's sarcoma in the elderly: a randomized study of oral etoposide versus vinblastine. *Cancer* 1994;74:2873-8.
66. Hauschild A, Petres-Dunsche C. Intraläsionäre Behandlung des klassischen Kaposi-sarkoms mit Interferon alpha. *Hautarzt* 1992;43:789-91.
67. Tur E, Brenner S. Classic Kaposi's sarcoma: low-dose interferon alfa treatment. *Dermatology* 1998;197:37-42.
68. Lev-Chelouche D, Abu-Abaid S, Merimsky O, et al. Isolated limb perfusion with high-dose tumor necrosis factor alpha and melphalan for Kaposi sarcoma. *Arch Surg* 1999;134:177-80.
69. Volm MD, Wenz J. Patients with advanced AIDS-related Kaposi's sarcoma (EKS) no longer require systemic therapy after introduction of effective antiretroviral therapy. *Proc Am Soc Clin Oncol* 1997;16:46a. abstract.
70. Santambrogio S, Ridolfo AL, Galli TM, Corbellino PM. Effect of highly active antiretroviral treatment (HAART) in patients with AIDS-associated KS. In: *Proceedings of the 12th World AIDS Conference, Geneva, June 28-July 3, 1998*;22275. abstract.
71. Wit FW, Sol CJ, Renwick N, et al. Regression of AIDS-related Kaposi's sarcoma associated with clearance of human herpesvirus-8 from peripheral blood mononuclear cells following initiation of antiretroviral therapy. *AIDS* 1998;12:218-9.
72. Robles R, Lugo D, Gee L, Jacobson MA. Effect of antiviral drugs used to treat cytomegalovirus end-organ disease on subsequent course of previously diagnosed Kaposi's sarcoma in patients with AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999;20:34-8.
73. Stelzer KJ, Griffin TW. A randomized prospective trial of radiation therapy for AIDS-associated Kaposi's sarcoma. *Int J Radiat Oncol Biol Phys* 1993;27:1057-61.
74. Volberding PA, Abrams DI, Conant M, Kaslow K, Vranizan K, Ziegler J. Vinblastine therapy for Kaposi's sarcoma in the acquired immunodeficiency syndrome. *Ann Intern Med* 1985;103:335-8.
75. Gill PS, Rarick M, McCutchan JA, et al. Systemic treatment of AIDS-related Kaposi's sarcoma: results of a randomized trial. *Am J Med* 1991;90:427-33.
76. Fischl MA, Krown SE, O'Boyle KP, et al. Weekly doxorubicin in the treatment of patients with AIDS-related Kaposi's sarcoma. *J Acquir Immune Defic Syndr* 1993;6:259-64.
77. Paredes J, Kahn JO, Tong WP, et al. Weekly oral etoposide in patients with Kaposi's sarcoma associated with human immunodeficiency virus infection: a phase I multicenter trial of the AIDS Clinical Trials Group. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;9:138-44.
78. Presant CA, Scolaro M, Kennedy P, et al. Liposomal daunorubicin treatment of HIV-associated Kaposi's sarcoma. *Lancet* 1993;341:1242-3.
79. Money-Kyrle JF, Bates F, Ready J, Gazzard BG, Phillips RH, Boag FC. Liposomal daunorubicin in advanced Kaposi's sarcoma: a phase II study. *Clin Oncol (R Coll Radiol)* 1993;5:367-71.
80. Uthayakumar S, Bower M, Money-Kyrle J, et al. Randomized cross-over comparison of liposomal daunorubicin versus observation for early Kaposi's sarcoma. *AIDS* 1996;10:515-9.
81. Gill PS, Wernz J, Scadden DT, et al. Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. *J Clin Oncol* 1996;14:2353-64.
82. Stewart S, Jablonowski H, Goebel FD, et al. Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. *J Clin Oncol* 1998;16:683-91.
83. Northfelt DW, Dezube BJ, Thommes JA, et al. Pegylated-liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. *J Clin Oncol* 1998;16:2445-51.
84. Belotti D, Vergani V, Drudis T, et al. The microtubule-affecting drug paclitaxel has antiangiogenic activity. *Clin Cancer Res* 1996;2:1843-9.
85. Saville MW, Lietzau J, Pluda JM, et al. Treatment of HIV-associated Kaposi's sarcoma with paclitaxel. *Lancet* 1995;346:26-8.
86. Gill PS, Tulpule A, Espina BM, et al. Paclitaxel is safe and effective in the treatment of advanced AIDS-related Kaposi's sarcoma. *J Clin Oncol* 1999;17:1876-83.
87. Welles L, Saville MW, Lietzau J, et al. Phase II trial with dose titration of paclitaxel for the therapy of human immunodeficiency virus-associated Kaposi's sarcoma. *J Clin Oncol* 1998;16:1112-21.
88. Groopman JE, Gottlieb MS, Goodman J, et al. Recombinant alpha-2 interferon therapy for Kaposi's sarcoma associated with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984;100:671-6.
89. Abrams DI, Volberding PA. Alpha interferon therapy of AIDS-associated Kaposi's sarcoma. *Semin Oncol* 1986;13:Suppl 2:43-7.
90. de Wit R, Danner SA, Bakker PJ, Lange JM, Eeftink Schattenkerk JK, Veenhof CH. Combined zidovudine and interferon-alpha treatment in patients with AIDS-associated Kaposi's sarcoma. *J Intern Med* 1991;229:35-40.

91. de Wit R, Schattenkerk JKME, Boucher CA, Bakker PJ, Veenhof KH, Danner SA. Clinical and virological effects of high-dose recombinant interferon-alpha in disseminated AIDS-related Kaposi's sarcoma. *Lancet* 1988;2:1214-7.
92. Lane HC, Kovacs JA, Feinberg J, et al. Anti-retroviral effects of interferon-alpha in AIDS-associated Kaposi's sarcoma. *Lancet* 1988;2:1218-22.
93. Volberding PA, Mitsuyasu R. Recombinant interferon alpha in the treatment of acquired immune deficiency syndrome-related Kaposi's sarcoma. *Semin Oncol* 1985;12:Suppl 5:2-6.
94. Krown SE, Paredes J, Bundow D, Polsky B, Gold JW, Flomenberg N. Interferon-alpha, zidovudine, and granulocyte-macrophage colony-stimulating factor: a phase I AIDS Clinical Trials Group study in patients with Kaposi's sarcoma associated with AIDS. *J Clin Oncol* 1992;10:1344-51.
95. Shepherd FA, Beaulieu R, Gelmon K, et al. Prospective randomized trial of two dose levels of interferon alfa with zidovudine for the treatment of Kaposi's sarcoma associated with human immunodeficiency virus infection: a Canadian HIV Clinical Trials Network study. *J Clin Oncol* 1998;16:1736-42.
96. Opravil M, Hirschel B, Bucher HC, Luthy R. A randomized trial of interferon-alpha2a and zidovudine versus bleomycin and zidovudine for AIDS-related Kaposi's sarcoma: Swiss HIV Cohort Study. *Int J STD AIDS* 1999;10:369-75.
97. Fife K, Howard MR, Gracie F, Phillips RH, Bower M. Activity of thalidomide in AIDS-related Kaposi's sarcoma and correlation with HHV8 titre. *Int J STD AIDS* 1998;9:751-5.
98. Soler RA, Howard M, Brink NS, Gibb D, Tedder RS, Nadal D. Regression of AIDS-related Kaposi's sarcoma during therapy with thalidomide. *Clin Infect Dis* 1996;23:501-5.
99. Saiag P, Pavlovic M, Clerici T, et al. Treatment of early AIDS-related Kaposi's sarcoma with oral all-trans-retinoic acid: results of a sequential non-randomized phase II trial. *AIDS* 1998;12:2169-76.
100. Guo WX, Gill PS, Antakly T. Inhibition of AIDS-Kaposi's sarcoma cell proliferation following retinoic acid receptor activation. *Cancer Res* 1995;55:823-9.
101. Nagpal S, Cai J, Zheng T, et al. Retinoid antagonism of NF-IL6: insight into the mechanism of antiproliferative effects of retinoids in Kaposi's sarcoma. *Mol Cell Biol* 1997;17:4159-68.
102. Gill PS, Espina BM, Moudgil T, et al. All-trans retinoic acid for the treatment of AIDS-related Kaposi's sarcoma: results of a pilot phase II study. *Leukemia* 1994;8:Suppl 3:S26-S32.
103. Bower M, Fife K, Landau D, Gracie F, Phillips RH, Gazzard BG. Phase II trial of 13-cis-retinoic acid for poor risk HIV-associated Kaposi's sarcoma. *Int J STD AIDS* 1997;8:518-21.
104. Lunardi-Iskandar Y, Bryant JL, Zeman RA, et al. Tumorigenesis and metastasis of neoplastic Kaposi's sarcoma cell line in immunodeficient mice blocked by a human pregnancy hormone. *Nature* 1995;375:64-8. [Erratum, *Nature* 1995;376:447.]
105. Gill PS, Lunardi-Iskandar Y, Louie S, et al. The effects of preparations of human chorionic gonadotropin on AIDS-related Kaposi's sarcoma. *N Engl J Med* 1996;335:1261-9. [Errata, *N Engl J Med* 1997;336:670, 1115.]
106. Krown SE. Kaposi's sarcoma — what's human chorionic gonadotropin got to do with it? *N Engl J Med* 1996;335:1309-10.
107. Kedes DH, Ganem D. Sensitivity of Kaposi's sarcoma-associated herpesvirus replication to antiviral drugs: implications for potential therapy. *J Clin Invest* 1997;99:2082-6.
108. Neyts J, De Clercq E. Antiviral drug susceptibility of human herpesvirus 8. *Antimicrob Agents Chemother* 1997;41:2754-6.
109. Martin DF, Kuppermann BD, Wolitz RA, et al. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. *N Engl J Med* 1999;340:1063-70.
110. Rivero J, Fraga M, Cancio I, Cuervo J, Lopez-Saura P. Long-term treatment with recombinant interferon alpha-2b prolongs survival of asymptomatic HIV-infected individuals. *Biotherapy* 1997;10:107-13.
111. Lane HC, Falloon J, Walker RE, et al. Zidovudine in patients with human immunodeficiency virus (HIV) infection and Kaposi sarcoma: a phase II randomized, placebo-controlled trial. *Ann Intern Med* 1989;111:41-50. [Erratum, *Ann Intern Med* 1990;112:388.]
112. Joffe MM, Hoover DR, Jacobson LP, Kingsley L, Chmiel JS, Visscher BR. Effect of treatment with zidovudine on subsequent incidence of Kaposi's sarcoma. *Clin Infect Dis* 1997;25:1125-33.