

HIV-Associated Kaposi's Sarcoma

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Kaposi's sarcoma (KS), currently the most common neoplasm associated with AIDS, was a rare occurrence prior to the onset of the AIDS epidemic. In 1872, Hungarian dermatologist Moritz Kaposi first described KS as an idiopathic multiple pigmented sarcoma. Three patterns of occurrence of KS were described before the AIDS epidemic. The most common pattern was an endemic form limited to sub-Saharan Africa that occurred

within a broad age range with varying severity. The second pattern, classic KS, occurred among older men of Mediterranean origin and commonly affected the skin of the lower extremities. Iatrogenic cases of KS constituted the third pattern and were mostly seen in immunosuppressed patients after transplantation or chemotherapy.¹

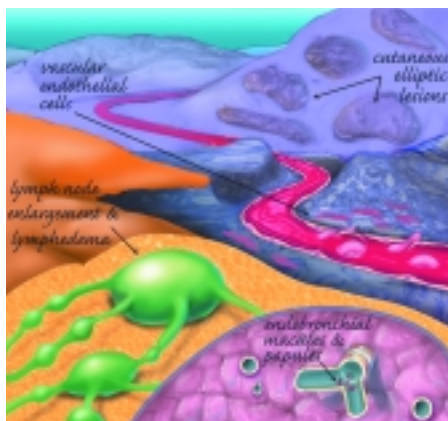
This article reviews the epidemiology, pathogenesis, and clinical presentation of KS in patients with HIV. Diagnosis, staging and prognosis, and treatment are also discussed.

EPIDEMIOLOGY

Sexual behavior as well as race have been associated in the epidemiology of KS associated with HIV.

Sexual Behavior

Epidemiologic studies have demonstrated a much higher incidence of KS in homosexual and bisexual men who are infected with HIV compared with patients who acquired HIV infection parenterally or through transfusion products or intravenous drug use.² Among HIV-positive homosexual men, 15% to 20% present with KS; in other HIV transmission groups, the incidence of KS is estimated at 1% to 3%.³ Also, women who acquired HIV infection through sexual contact with bisexual men are more likely to develop KS compared with women in other HIV transmission groups. KS has also been reported to occur in HIV-negative homosexual men.³



A review of the epidemiology of KS reveals that the percentage of patients with AIDS who present with KS has declined compared with the percentage in the early years of the AIDS epidemic. Various theories (eg, changing patterns of sexual behavior; decreasing incidence of sexually transmitted diseases) have been postulated to explain the decline of KS; however, the overall number of cases has essentially remained stable because of the general increase

in the total number of patients with AIDS.³

KS has been associated with increased sexual activity in most studies. The number of sexual partners and history of prior sexually transmitted infection has been most consistently identified as a risk factor for KS.¹ KS has also been linked to an increased frequency of anal sex and receptive anal intercourse.²

Race

Black men are less likely to develop KS compared with white men.³ This finding, which has not been uniformly confirmed, may be related to a difficulty recognizing KS lesions in patients with dark skin; socioeconomic factors that result in decreased access to medical services and low reporting rates may also explain this finding.³

PATHOGENESIS

Expression of Cytokines

Tremendous progress has been made toward understanding the pathogenesis of KS and its association with HIV infection. HIV infection contributes to the

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pathogenesis by causing profound immunosuppression as well as loss or impairment of CD4 cell function.⁴ HIV infection also causes an immune dysregulation by altering the expression of cytokines, including interleukin-1, tumor necrosis factor- α , and interleukin-6.³ These cytokines, which are present in the blood of patients infected with HIV, have been shown to induce vascular endothelial cells to assume the characteristic spindle shape. In addition, *in vitro* studies have demonstrated that the cytokines secrete a number of angiogenic growth factors (eg, basic fibroblast growth factor). Finally, protein derived from HIV-1 virus, the transactivating protein HIV Tat, has been shown to be a mitogen that, in synergistic combination with basic fibroblast growth factor, results in the induction and proliferation of cells derived from KS.⁵ Several other mitogens, which include oncostatin M, interleukin-6, and scatter factor, have been identified from cultured KS tumor cells, which suggests an involvement in the pathogenesis of KS. Integrins and the apoptosis process have been found to be important for the proliferation and neovascularization of KS tumor cells.⁵

Kaposi's Sarcoma-Associated Herpesvirus

Strong evidence has etiologically linked KS to a sexually transmitted virus (human herpesvirus 8, also termed *Kaposi's sarcoma-associated herpesvirus* [KSHV]) that is a member of the gamma herpesvirus family. Chang et al⁶ first demonstrated that more than 90% of HIV-KS tissue samples were positive for herpesvirus-like DNA sequences. Additional laboratories have confirmed these findings through polymerase chain reaction and other methods. KSHV genomic DNA has been found in the lesions, semen, and peripheral blood of patients with KS.⁷ KSHV DNA has also been detected in KS skin lesions of homosexual men who are not infected with HIV, as well as in patients with classic and African (endemic) forms of KS.⁴

In patients with KSHV, histologic examination typically reveals proliferation of a spindle cell population, which forms slit-like vascular spaces that often contain extravasated erythrocytes. Frequently a pleomorphic mixture of spindle cells, fibroblasts, endothelial cells, inflammatory cells, and evidence of neovascularization is seen.⁸

CLINICAL PRESENTATION

KS associated with HIV has a variable clinical course ranging from minimal disease that is discovered incidentally to aggressive growth with significant morbidity and mortality. The skin is the most common site of initial presentation; however, cutaneous involvement may

occasionally be absent. Cutaneous symptoms may even be preceded by nodal, oral, or visceral KS.

Cutaneous Presentation

Cutaneous KS lesions vary in size, characteristics, and number. Some patients present with a small number of isolated lesions whereas other patients may have widespread cutaneous involvement (**Figure 1**). Lesions range from millimeter-sized macules and papules to large confluent nodules that are 10 cm or larger. The color also ranges from faint pink to red-violet to brown. Chronic lesions usually appear dark violaceous brown. In patients with dark or olive-colored skin, lesions may appear very dark or almost black.³ Yellow perilesional halos are often seen. The lesions are often elliptical and may be arranged linearly and symmetrically along skin tension lines.⁹ Usually the lesions are non-pruritic and painless; however, large lesions may become painful. The skin surrounding new or enlarging lesions may be ecchymotic or edematous. The edema is generally nonpitting and commonly occurs in the lower extremities (**Figure 2**). Edema may also occur in the periorbital region, face, genitalia, and other body sites.³

Plaque-like lesions may also occur. These lesions are similar to nodules but are more extensive locally, suggesting the coalescence of multiple nodules. The plaque-like lesions occur on the thighs, calves, or soles of the feet and may be exophytic and fungating with breakdown of overlying skin.⁸ The lesions are often complicated with lymphedema, which may occur as a relatively isolated finding and may be out of proportion to the extent of the visible cutaneous disease. Plaque-like lesions may ulcerate, bleed, or become a focus for secondary bacterial infection.

Nodal Presentation

Lymph node involvement in patients with KS is quite common and may occur in the absence of cutaneous disease. Massive lymph node enlargement and lymphedema may develop. Because no clinical characteristics distinguish lymphadenopathic KS from disorders such as lymphoma and tuberculosis, a fine-needle aspiration cytology and an open biopsy may be necessary.⁸

Oral Presentation

Oral lesions have been reported in 33% to 71% of patients with KS.¹⁰ Oral lesions are the initial presentation of KS in 15% of patients. Lesions range from flat, red to violet papules (**Figure 3**) to exophytic, ulcerative nodules. Lesions most commonly occur on the palate (53%), oropharynx (15%), and gingiva (11%), but may



Figure 1. Photograph of widespread cutaneous Kaposi's sarcoma in a patient infected with HIV. Adapted with permission from Cohen PT, Sande MA, Volberding PA, eds: *The AIDS Knowledge Base: A Textbook on HIV Disease from the University of California, San Francisco and San Francisco General Hospital*, 2nd ed. Boston: Little, Brown, 1994: plate 5.5-9.



Figure 2. Photograph of pedal edema and plaques caused by Kaposi's sarcoma in a patient infected with HIV. Adapted with permission from Cohen PT, Sande MA, Volberding PA, eds: *The AIDS Knowledge Base: A Textbook on HIV Disease from the University of California, San Francisco and San Francisco General Hospital*, 2nd ed. Boston: Little, Brown, 1994: plate 5.5-10.

involve any part of the mucosal surface including the tongue, tonsillar pillars, floor of the mouth, pharynx, or trachea. Trauma during normal chewing may cause pain, bleeding, ulceration, and secondary infection. Bulky lesions may interfere with nutrition and speech.

Laryngeal involvement has also been reported; the most common laryngeal site is the epiglottis. Laryngeal KS is almost always associated with cutaneous lesions. Common presenting symptoms of laryngeal KS may include pain, bleeding, dysphagia, speech abnormalities, and airway compromise. Laryngeal KS is an important consideration in the diagnosis of any pigmented lesion of the larynx in a patient with HIV infection. Early detection and management is essential because laryngeal KS is associated with severe bleeding, airway obstruction, and death.

Visceral Presentation

Pulmonary involvement. Pulmonary KS is an important consideration in the diagnosis of HIV-infected patients with respiratory symptoms or abnormal chest radiograph findings, especially in the presence of cutaneous KS. Pulmonary involvement has been report-



Figure 3. Photograph of Kaposi's sarcoma of the gingiva. Adapted with permission from Cohen PT, Sande MA, Volberding PA, eds: *The AIDS Knowledge Base: A Textbook on HIV Disease from the University of California, San Francisco and San Francisco General Hospital*, 2nd ed. Boston: Little, Brown, 1994: plate 5.5-12.

ed in 18% to 40% of patients with cutaneous KS; however, 38% to 75% of patients with cutaneous KS demonstrated pulmonary involvement in an autopsy series.¹¹ Almost all intrathoracic structures including the tracheo-bronchial tree, pulmonary parenchyma, and pleura may



Figure 4. Photograph of multiple subcutaneous bacillary angiomatosis nodules in a patient with concomitant Kaposi's sarcoma of the medial canthus of the left eye. Adapted with permission from Cohen PT, Sande MA, Volberding PA, eds: *The AIDS Knowledge Base: A Textbook on HIV Disease from the University of California, San Francisco and San Francisco General Hospital*, 2nd ed. Boston: Little, Brown, 1994: plate 6.3-4.

be involved; the lymph nodes, heart, and pericardium may also be involved but to a lesser extent. The higher frequency of pulmonary KS revealed during post-mortem examination compared with antemortem examination suggests that the disease is insidious and remains asymptomatic in a large number of patients.

Common presenting symptoms of pulmonary KS include cough, hemoptysis, shortness of breath, pleuritic chest pain, and fever. Results of physical examination may be normal or nonspecific with the presence of crackles or wheeze related to involvement of the upper respiratory tract. Pulmonary involvement usually occurs as a late manifestation of HIV disease, although it may occur at any stage of HIV.¹¹

Gastrointestinal involvement. In patients with KS, gastrointestinal (GI) involvement has been reported in up to 40% of patients at initial diagnosis and in up to 80% of patients at autopsy.³ GI involvement may occur in the absence of cutaneous lesions, and many patients with KS and GI involvement remain asymptomatic. Patients with GI lesions may present with nausea, vomiting, abdominal pain, weight loss, upper and lower GI bleeding, or intestinal obstruction.⁹

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Initial Evaluation

Careful examination at each office visit of the skin and oral cavities of patients with HIV infection is the key to early diagnosis of KS. Initial evaluation of a patient with suspected KS includes a thorough general medical history with specific attention to duration and rate of development of skin lesions and respiratory and GI symptoms. History of opportunistic infections and HIV treatment is also relevant. The history should be followed by a detailed physical examination with special attention to those areas frequently affected by the disease (eg, lower extremities, face, oral mucosa, GI tract, and lungs).

Cutaneous Disease

The presumptive diagnosis of cutaneous KS can be made by a trained observer. However, considering the variety of clinical conditions that may mimic cutaneous KS, a skin biopsy is essential to establish a diagnosis.

Differential diagnosis. High on the list of differential diagnoses for cutaneous KS is bacillary angiomatosis (BA), a skin condition caused by the *Bartonella* species, a gram-negative bacillus that is treatable with antibiotics. BA skin lesions are usually raised, red, and round papules or nodules. BA may be associated with systemic symptoms such as fever, chills, malaise, headache, and anorexia. BA skin lesions and KS skin lesions may coexist (**Figure 4**).

Other less common conditions that may mimic KS lesions are cutaneous *Pneumocystis carinii* infection, fungal infections, bacterial cellulitis, or folliculitis.⁸ In the early stages, KS lesions may be mistaken for purpuras, hematomas, angiomas, dermatofibromas, or nevi.⁹

Nodal Disease

As noted in the discussion of nodal presentation, because no clinical characteristics distinguish lymphadenopathic KS from disorders such as lymphoma and tuberculosis, a fine-needle aspiration cytology and an open biopsy may be necessary.⁸

Oral Disease

Diagnosis of oral disease is generally made by the classic clinical appearance of a lesion. A biopsy of the lesion confirms diagnosis of KS in questionable cases.

Visceral Disease

The possibility of the coexistence of several diseases in patients with KS cannot be overemphasized.

Pulmonary disease. As noted previously for patients with pulmonary manifestations of KS, the results of

physical examination may be normal or nonspecific with the presence of crackles or wheeze related to involvement of the upper respiratory tract.

Differential diagnosis. The differential diagnoses for respiratory symptoms in an HIV-positive patient primarily include opportunistic infections and pulmonary KS, especially in the presence of cutaneous KS. Bronchoscopic visualization serves as the gold standard for diagnostic differentiation. In addition, bronchoalveolar lavage also helps to rule out concomitant infection. Endobronchial visualization reveals a characteristic appearance of single to multiple cherry red to violaceous macules or papules typically located at the bifurcation of the trachea.¹² A biopsy of the lesions may not be diagnostic, and a presumptive diagnosis of KS can be made only by visualization of typical lesions. Bronchoscopy can be reserved for patients with an abnormal result on radiography and persistent respiratory symptoms in whom no other cause is found. Bronchoscopic examination may be negative if parenchymal or pleural involvement occurs in the absence of tracheobronchial lesions; in such patients, transbronchial or open lung biopsy may be indicated.

Gallium-thallium scanning is a very useful adjunct to differentiate KS from other opportunistic infections. KS is thallium avid and gallium negative, whereas the opposite is true for infections, which are gallium avid and thallium negative. After exclusion of infection as the cause of clinical findings, treatment decisions in the presence of respiratory symptoms are based on the radiologic findings and the extent of bronchoscopic disease.

Chest radiography. The chest radiograph is normal in 5% to 20% of patients with pulmonary KS. However, the malignancy may be detected as an incidental finding on the radiograph. Perihilar linear density and single or multiple nodular opacity with no preferential distribution are commonly reported abnormalities.¹² Less frequent are segmental, lobar, alveolar, or interstitial infiltrates and hilar or mediastinal lymphadenopathy. The middle and lower lung zones are commonly affected. Isolated upper lobe or apical involvement has not been reported; such an occurrence would indicate the presence of other concomitant pathology. Pleural effusion is usually large and bilateral when present. These radiographic findings are usually nonspecific and cannot be used to distinguish pulmonary KS from opportunistic infections.

Computed tomography. CT is increasingly being used to establish the diagnosis of pulmonary KS. The most common abnormalities reported on CT are poorly defined parenchymal nodules with no zonal predilec-

tion. Perihilar infiltrates occurring in a bronchovascular distribution are another characteristic finding. Fissural nodularity and fissural distortion represent perilymphatic spread of the tumor. Tumor masses, mediastinal and hilar lymph node involvement, and pleural effusion are other associated findings. Perinodal haze or areas of ground-glass attenuation around the nodules have also been reported. Although none of these findings alone are specific for the diagnosis of pulmonary KS, the presence of a combination of these findings is highly suggestive of the diagnosis.¹¹

Gastrointestinal disease. Testing the stool for occult blood is an excellent screening method for GI involvement in KS. Lesions can be visualized on endoscopy, which typically reveals isolated or confluent hemorrhagic nodules varying in size from 0.5 to 10 cm. The lesions may occur in any part of the GI tract. Endoscopic biopsy may be negative because lesions are often submucosal.

STAGING AND PROGNOSIS

The staging of HIV-associated KS was developed by the AIDS Clinical Trial Group of the National Institute of Health.¹³ This system divides patients into good and poor risk groups (**Table 1**) based on three parameters: tumor bulk, immune status, and severity of illness.¹³ Patients in the poor risk group are associated with a poor prognosis. Features associated with a short survival include a low CD4 count (less than 200 cells/ μ L), prior history of opportunistic infection, bulky HIV-KS involving a mucosal surface (eg, mouth, GI tract) or causing edema, B symptoms (ie, unexplained fever, night sweats, involuntary weight loss of more than 10% of body weight, or diarrhea persisting longer than 2 weeks), and a Karnofsky performance score of less than 70%.

TREATMENT

The primary goals of therapy for KS are palliation of symptoms, prevention of disease progression, and cosmetic improvement. The current consensus for treatment favors an individualized approach that bases treatment decisions on the extent and rate of tumor growth, the presence or absence of visceral involvement, and patient symptoms. Treatment may be initiated when KS lesions have developed at anatomic sites that are severely disfiguring or socially stigmatizing for the patient, when painful or bulky lesions on the plantar surface of the feet interfere with ambulation, and when intra-oral or pharyngeal lesions interfere with eating.⁸ Therapy is also initiated if the patient develops lymphedema (the lymphedema may not always correlate with the bulk of

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Table 1. Staging Classification for AIDS-Related Kaposi's Sarcoma

Parameter	Good Risk (all of the following symptoms)	Poor Risk (any of the following symptoms)
Tumor bulk	Confined to skin and/or lymph nodes and/or minimal oral disease (non-nodular KS confined to palate)	Tumor-associated edema or ulceration; extensive oral KS; gastrointestinal KS; KS in other non-nodal viscera
Immune status	CD4 count \geq 200 cells/ μ L	CD4 count < 200 cells/ μ L
Severity of illness	No history of opportunistic infection or thrush; no B symptoms*; Karnofsky Performance Status \geq 70	History of opportunistic infection and/or thrush; B symptoms* present; Karnofsky Performance Status < 70; other HIV-related illness (eg, neurologic disease, lymphoma)

KS = Kaposi's sarcoma.

*Unexplained fever, night sweats, involuntary weight loss (>10%), or diarrhea persisting longer than 2 weeks.

Adapted with permission Krown SE, Metroka C, Wernz JC: Kaposi's sarcoma in the acquired immune deficiency: a proposal for uniform evaluation, response, and staging criteria. *J Clin Oncol* 1989;7:1201-1207.

the disease) or symptomatic visceral involvement (pulmonary KS can have an especially rapid progression to severe respiratory compromise and death).⁸ A variety of local and systemic treatment options are available. Because of the potential toxicities of systemic treatment, local treatment should be preferred whenever possible. Investigational therapies are also discussed.

Local Therapy

Widely used conventional approaches for local therapy include cryotherapy, intralesional chemotherapy, radiation therapy, and topical therapy.

Cryotherapy. Cryotherapy can be used to effectively treat small, cosmetically disfiguring lesions (eg, facial lesions). Macular and papular lesions smaller than 1 cm exhibit the best response; however, cryotherapy can be used effectively in nodular lesions up to 2 cm. Treatment involves the application of liquid nitrogen to local KS lesions; treatment may be repeated at 3-week intervals. Side effects include minor pain and blistering. Cryotherapy may also leave a flat white scar; in patients with dark skin, the scar may look cosmetically worse than the original lesion.¹⁴ Recurrence may be a problem during the treatment of large lesions.

Intralesional chemotherapy. Intralesional chemotherapy can be used to treat oral lesions and cutaneous lesions larger than 2 cm. Vinblastine is the most widely used pharmacologic agent in intralesional chemotherapy. The recommended dose of vinblastine is 0.2 mg/mL of solution injected for every 0.5 cm of lesion; the dose should not exceed 4 mL. The treatment can be repeated in 4 weeks.¹⁵ Tumor regression can be expected within 3 weeks. Response rates of 74% to 88% have been reported, with a median duration of

response between 4 to 7 months. Common side effects of intralesional vinblastine are ulceration, pain, and secondary infection. Pain develops approximately 12 hours after treatment and can last up to 48 hours. To alleviate the pain, lidocaine may be added to the vinblastine treatment regimen; lidocaine has been shown not to alter the efficacy or tolerance of the treatment. Epilation may also occur; thus intralesional chemotherapy should be avoided in hair-bearing areas.

Radiation therapy. Radiation therapy is an effective mode of local treatment for patients with minimal or localized KS. Radiation therapy is also well suited for the relief of local symptoms in patients who are unresponsive to or have contraindications to systemic chemotherapy and in patients with a relatively short life expectancy (ie, less than 2 months). Radiation therapy may be used in the treatment of oral and pharyngeal lesions. Radiation therapy not only improves function and cosmetic appearance but also alleviates pain, bleeding, and, to a lesser extent, helps to relieve edema.

In radiation therapy, low-energy electron beams or superficial radiology are used to treat small, superficial, flat lesions. This treatment approach carries the advantage of a smaller amount of tissue penetration, which spares the deeper structures from irradiation. High energy radiology, termed *megavoltage therapy*, is used to treat larger nodular or plaque-like lesions as well as lesions with considerable edema.

Various dosing schemes can be employed that range from single-dose to fractionated regimens, depending on the site and size of the lesion and the goal of treatment. Single doses of 8 Gy may be used to treat small to moderate cutaneous lesions of the face, arms, and trunk. Single-dose regimens can also provide rapid

Table 2. Single-Agent Chemotherapy Regimens for the Treatment of Kaposi's Sarcoma

Drug	Dose	Response Rate, %	Median Duration of Response
Vinblastine	4 mg/wk given intravenously to start; increase by 2 mg/wk; median dose, 6 mg/wk	25-30	9 wk
Vincristine	2 mg/wk for 2-5 wk; decrease to 2 mg every other week	20-59	> 4 mo
Teniposide	360 mg/m ² every 3 wk	40	9 wk
Etoposide	150 mg/m ² /day for 3 days every 4 wk	76	9-9.5 mo
Bleomycin	6 mg/m ² /day continuous infusion for 4 days every 4 wk	48	7 mo
	5 mg given intramuscularly once daily for 3 days every 3 wk	74	20 wk
	20 mg/m ² /day continuous infusion for 3 days	41-65	3 mo
Doxorubicin	15 mg/m ² every 2 wk	48	NA
Liposomal doxorubicin	20 mg/m ² given intravenously every 3 wk	90	9 wk
Liposomal daunorubicin	40 mg/m ² given intravenously every 2 wk	75	NA
Paclitaxel	135-175 mg/m ² every 3 wk	65	10 wk

NA = not available.

palliation of symptoms for patients with poor prognosis and short life expectancy. In patients with longer expected survival times, protracted, fractionated regimens can produce an effective and more durable response. Studies have reported fractionated dosages of up to 40 Gy with response rates in up to 83% of patients;¹⁶ other studies have recommended that a total dose of 24 Gy is equally effective and also less toxic, which would permit safe treatment of recurrence.

Side effects of radiation therapy include erythema and desquamation of skin, painful blisters on the soles of feet, oral mucositis, and residual pigmentation after resolution of active disease. The lower extremities are prone to brawny induration with obstruction of lymphatic flow.

Topical therapy. On February 3, 1999, the United States Food and Drug Administration approved alitretinoin 0.1% for topical treatment of cutaneous KS lesions in HIV-infected patients. Alitretinoin, which inhibits the growth-promoting effects of oncostatin M on KS cells, has a dose-dependent inhibitory effect on the growth of KS cells in vitro.

Systemic Therapy

Chemotherapy. Chemotherapy is the treatment of choice for visceral or widespread cutaneous KS lesions. Widely used agents include vinca alkaloids (vincristine and vinblastine), etoposide, teniposide, liposomal anthracyclines (doxorubicin and daunorubicin), and paclitaxel. In addition, interferon- α has been used as a

single agent as well as a part of combination regimens in the treatment of KS. Response rates range from 10% to 75% for single-agent chemotherapy (Table 2), and 50% to 88% for combination chemotherapy (Table 3). The wide variation in response rates does not solely reflect the efficacy of the drug or the regimen; the variation is largely caused by the patient's immune status, tumor burden, and above all, the lack of universally applied criteria for evaluation of response.

The combination of doxorubicin, bleomycin, and vincristine (ABV) has been widely reported with response rates up to 88%. Recently, two large multicenter trials evaluated ABV regimens compared with the liposomal anthracyclines doxorubicin and daunorubicin.¹⁵ In these trials, the liposomal agents exhibited an equivalent or better response compared with the combination regimen of ABV. However, the liposomal agents demonstrated a better side effect profile. The occurrence of peripheral neuropathy and alopecia was reported to be 36% and 41%, respectively, in the ABV patients compared with 8% and 13%, respectively, in the daunorubicin patients. The occurrence of neutropenia was the same in both treatment groups.

Highly active antiretroviral therapy. The association between immunosuppression and KS has long been appreciated. Recent studies in HIV-infected patients with KS have demonstrated a response to highly active antiretroviral therapy (HAART). This therapy, which consists of two nucleoside analogues and a protease inhibitor, has been shown to decrease HIV plasma levels,

Table 3. Combination Chemotherapy Regimens for the Treatment of Kaposi's Sarcoma

Regimen	Dose	Response Rate, %	Median Duration of Response
Vincristine/vinblastine	2 mg vincristine given intravenously every other wk alternating with 0.1 mg/kg vinblastine every other wk	43	> 35 wk
Bleomycin/vincristine or vinblastine	30 mg bleomycin, 2 mg vincristine or 2.5-5 mg vinblastine every 3 wk	57	5 mo
Doxorubicin/bleomycin/vincristine	20 mg/m ² doxorubicin, 10 mg/m ² bleomycin, 1.4 mg/m ² vincristine every 2 wk	88	9 mo

increase CD4 T cell count, decrease the incidence of opportunistic infections, and improve overall short-term mortality. Clinical trials of the effectiveness of HAART in the treatment of patients with HIV-KS have reported 50% decreases in disease progression and mortality in the short-term period (1 year to 3 years).¹⁷ The length of time that HAART can effectively suppress viral replication is not yet known. However, complete resolution of cutaneous KS has been reported after the initiation of HAART.¹⁷ The effective inhibition of HIV replication and restoration of immune function are speculated to contribute to the regression of KS. In addition, protease inhibitors may have a direct antiviral effect on human herpesvirus 8.¹⁷ This hypothesis is supported by a case report of an HIV-infected patient whose human herpesvirus 8 resolved after the initiation of HAART.¹⁷

Investigational Therapies

Recent developments in the pathogenesis of AIDS-related KS have revealed the complex and multifactorial nature of this disorder, and numerous studies are currently evaluating new therapeutic agents. These therapeutic approaches include the enhancement of immune function, anti-human herpesvirus 8 therapy, immunostimulatory cytokines (eg, interleukin-1, interleukin-6, tumor necrosis factor), and hormonal manipulations. Investigational local approaches include interferon- α , myeloid colony-stimulating factors, sclerosing agents, recombinant platelet factor 4, and chorionic gonadotropin. In the future, some of these therapeutic approaches may become the focus of research to further develop treatment and preventive measures.

SUMMARY

KS may present at any point in the course of HIV infection. HIV-associated KS has an unpredictable course that ranges from a small number of stable lesions to explosive progression of disease activity.

Increasing evidence suggests that a putative transmissible agent and immune dysregulation are involved in pathogenesis. KS is usually not the direct cause of mortality in the patients, although the disease is associated with significant morbidity. Treatment measures are usually aimed at improving the quality of life. Treatment goals are tailored to the individual patient and may range from cosmesis to control of disseminated disease and prevention of KS progression. Further advances toward a more clear understanding of the pathogenesis of KS may contribute significantly to the therapeutic approaches of this enigmatic disease. **HP**

REFERENCES

1. Jacobson LP, Armenian HK: An integrated approach to the epidemiology of Kaposi's sarcoma. *Curr Opin Oncol* 1995;7:450-455.
2. Grulich AE, Kaldor JM, Hendry O, et al: Risk of Kaposi's sarcoma and oroanal sexual contact. *Am J Epidemiol* 1997;145:673-679.
3. Krown SE: Acquired immunodeficiency syndrome-associated Kaposi's sarcoma: biology and management. *Med Clin North Am* 1997;81:471-494.
4. Miles SA: Pathogenesis of AIDS-related Kaposi's sarcoma: evidence of a viral etiology. *Hematol Oncol Clin North Am* 1996;10:1011-1021.
5. Nickoloff BJ, Foreman KE: Charting a new course through the chaos of KS. *Am J Pathol* 1996;148:1323-1329.
6. Chang Y, Cesarman E, Pessin MS, et al: Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 1994;266:1865-1869.
7. Huang YQ, Li JJ, Poiesz BJ, et al: Detection of the herpesvirus-like DNA sequences in matched specimens of semen and blood from patients with AIDS-related Kaposi's sarcoma by polymerase chain reaction in situ hybridization. *Am J Pathol* 1997;150:147-153.
8. Cohen PT, Sande MA, Volberding PA, eds: *The AIDS Knowledge Base: A Textbook on HIV Disease from the University of California, San Francisco and San Francisco General Hospital*, 2nd ed. Boston: Little, Brown, 1994:7.1-1-7.3-11.

9. Dezube BJ: Clinical presentation and natural history of AIDS-related Kaposi's sarcoma. *Hematol Oncol Clin North Am* 1996;10:1023-1029.
10. Schiff NF, Annino DJ, Woo P, Shapshay SM: Kaposi's sarcoma of the larynx. *Ann Otol Rhinol Laryngol* 1997; 106:563-567.
11. Huang L, Schnapp LM, Gruden JF, et al: Presentation of AIDS-related pulmonary Kaposi's sarcoma diagnosed by bronchoscopy. *Am J Respir Crit Care Med* 1996;153: 1385-1390.
12. Cadrenal J, Mayaud C: AIDS and the lung: update 1995. 3. Intrathoracic Kaposi's sarcoma in patients with AIDS. *Thorax* 1995;50:407-414.
13. Krown SE, Metroka C, Wernz JC: Kaposi's sarcoma in the acquired immune deficiency: a proposal for uniform evaluation, response, and staging criteria. *J Clin Oncol* 1989;7:1201-1207.
14. Millar JL, Goldstein D, Gelmon KA: Managing HIV, treating secondary outcomes: HIV and Kaposi's sarcoma. *Med JAust* 1996;164:539-542.
15. Lee F, Mitsuyasu RT: Chemotherapy of AIDS-related Kaposi's sarcoma. *Hematol Oncol Clin North Am* 1996;10:1051-1068.
16. Swift PS: The role of radiation therapy in the management of HIV-related Kaposi's sarcoma. *Hematol Oncol Clin North Am* 1996;10:1069-1080.
17. Aboulafia DM: Regression of acquired immunodeficiency syndrome-related pulmonary Kaposi's sarcoma after highly active antiretroviral therapy. *Mayo Clin Proc* 1998;73:439-443.

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