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# MANAGEMENT OF KAPOSI'S SARCOMA ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

## Report Prepared by
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# 1. INTRODUCTION

Kaposi's sarcoma (KS) was first described in 1872 by the Hungarian dermatologist Dr. Moriz Kaposi, as "idiopathic multiple pigmented sarcomas of the skin." In its classic form, KS is an uncommon malignancy occurring primarily in elderly men of Mediterranean or eastern European Jewish origin. The disease is usually confined to the lower extremities and commonly runs an indolent course lasting from 10 to 15 years or longer.

Since the early 195Os, KS has also been recognized as a common neoplasm in equatorial Africa, occurring mainly in young males between the ages of 25 and 40. The endemic African form of KS pursues a much more aggressive course than classical KS. Even when localized, it frequently grows as a rapidly progressive fungating exophytic tumour, or spreads by diffuse infiltration of surrounding tissues and may even invade bone. In young adolescents, the disease often presents with generalized lymphadenopathy and visceral involvement. The prognosis of this form of KS is extremely poor, with almost 100 percent mortality within the first three years.

Kaposi's sarcoma has been associated with both congenital and acquired immunodeficiency and is one of the tumours most frequently seen in patients who are receiving immunosuppressive therapy following organ transplantation. The incidence of KS in this group of patients has been estimated to be from 150 to 200 times that of the general population.

The unusual occurrence of KS in young homosexual men in California and New York led to the identification of acquired immunodeficiency syndrome (AIDS) in 1981. KS is the most common tumour associated with human immunodeficiency virus (HIV) infection and is commonly called epidemic Kaposi's sarcoma (EKS). The clinical presentation and course of HIV-associated KS is quite distinct, even though it is histopathologically indistinguishable from classical or endemic African KS.

This report briefly discusses the etiology and diagnosis of Kaposi's sarcoma. It also describes the variations in the clinical presentation of the disease and the treatment strategies common to all KS patients.

# 2. ETIOLOGY

The etiology of EKS is as yet unknown. The disease is probably multifactorial. An increased frequency of the human leukocyte antigen DR5 (HLA-DR5) has been identified in classical KS, suggesting a genetic predisposition, but the same association has not been established for EKS.

The role that other agents play in the development of EKS remains unclear. Although HIV infection is a prerequisite for the development of the immunodeficiency that predisposes patients to the development of KS, there is no evidence to suggest that HIV is a direct causative agent. Cytomegalovirus (CMV) infection occurs frequently in homosexual men, but research has failed to prove this virus plays a causal role in KS. Recent epidemiologic evidence from the United States, Europe, and Canada has suggested the possibility of a sexually transmitted agent (not yet identified) that acts as a cofactor for EKS.

Recent observations suggest the EKS is not a classic monoclonal metastasizing neoplasm, but rather a multicentric tumour that arises as a result of disordered growth regulation in the vascular endothelium. KS cells in culture are known to produce substances that stimulate the growth of both EKS tumour cells and normal vascular cells. Extensive research is currently underway to define the role that these autocrine growth factors play in the development of EKS.

# 3. DIAGNOSIS OF KAPOSI'S SARCOMA

The definitive diagnosis of KS is made on histologic examination of biopsy material, even though the disease is easy to recognize clinically. Obtaining specimens is not usually difficult, as cutaneous lesions predominate in most patients and are readily available for biopsy. Classical, endemic African, and HIV-associated KS are all similar in histologic appearance despite their extremely variable clinical presentations.

Microscopic examination of KS tissue samples reveals a proliferation of endothelium-lined, vascular slits, surrounded by interweaving bundles of spindle-shaped cells. A mononuclear cell infiltrate of lymphocytes and plasma cells may be present in KS tissue samples in addition to extravasated erythrocytes and hemosiderin-laden macrophages.

# 4. CLINICAL PRESENTATION

The initial presentation and clinical course of HIV-associated KS is extremely variable. The median age of patients presenting with KS is approximately 37 years. The range is from the late teens to the mid 60s. The malignancy is seen most frequently in homosexual or bisexual men, but it has been reported in all subgroups at risk for HIV infection. Approximately 25 percent of all homosexual males with AIDS will develop KS during the course of their illness. By contrast, KS occurs in less than five percent of AIDS sufferers who are heterosexual intravenous drug abusers, hemophiliac patients, or recipients of blood transfusions. It is interesting to note that the percentage of AIDS patients with KS has fallen steadily over the past decade. As yet, there is no explanation for this change in incidence.

## Cutaneous Manifestations

In more than 90 percent of patients, Kaposi's sarcoma involves the skin. The cutaneous lesions are easily recognizable, although the differential diagnosis of early lesions includes ecchymoses, nevi, insect bites, dermatofibroma, or even acne. Characteristically, the lesions start as small reddish or purple nodules that may appear on the trunk, the face, including the conjunctiva, and the upper and lower extremities, including the hands and feet (Plates 1 and 2). Early lesions may be surrounded by a pale yellow halo. They may range in diameter from a few millimetres (Plate 3) to several centimetres (Plate 4). Occasionally, multiple lesions can coalesce to form large plaques and, less frequently, may form a large, localized infiltrating lesion (Plate 5). The lesions are usually painless and asymptomatic, although exophytic lesions on the feet may bleed and may interfere with walking or the wearing of shoes.

Cutaneous involvement may be quite limited, with only a few isolated lesions. The lesions may progress slowly in size and number over the course of many months or even years. On the other hand, some patients present with widespread, rapidly proliferating KS disease, associated with the daily appearance of multiple new lesions. Advanced disease is often associated with significant edema even in the absence of papable lymph node involvement.

## Lymph Node Involvement

Lymphadenopathy is commonly seen in patients with EKS. The true incidence of nodal involvement by this tumour is not known, as many processes associated with HIV infection cause lymphadenopathy, and biopsy for confirmation is seldom performed. Lymphadenopathy is asymptomatic for most patients but, on occasion, extensive involvement of the nodes by KS may produce severe local edema.

## Mucosal Involvement of the Aero-Digestive Tract

Nearly 50 percent of patients with KS have involvement of the gastrointestinal (GI) tract and, for almost all of these, GI involvement occurs in association with cutaneous lesions.

Lesions frequently occur on the mucous membranes of the soft or hard palate of the mouth. Less frequently, the tongue, tonsils and gums may be involved. In the early stages, cutaneous lesions are usually flat and asymptomatic, but they may progress to form symptomatic nodules (Plate 6). At symptomatic nodule stage, the lesions may ulcerate and bleed and may interfere with speaking, chewing, swallowing, and maintaining proper oral hygiene.

The esophagus, stomach, duodenum, colon and rectum may all be involved. Most frequently, such GI involvement is asymptomatic. In advanced cases, though, lesions of the upper GI tract cause dysphagia, epigastric pain, early satiety, symptoms of gastric outlet obstruction, and occasionally, hematemesis or melena. Lesions of the lower GI tract may produce abdominal cramps, diarrhea, rectal pain, or rectal bleeding. Barium studies may demonstrate the lesions (Plate 7), but endoscopy is the investigation of choice to confirm KS involvement of the GI tract. Early lesions may be flat, but more advanced lesions (those that give rise to symptoms) are usually raised, sessile red nodules that may or may not be ulcerated (Plate 8). In the absence of symptoms, endoscopy is not necessary; the identification of minimal GI involvement does not alter patient management or prognosis.

KS may also involve the trachea and bronchial tree. Early lesions are usually asymptomatic, being identified at bronchoscopy performed to investigate other pulmonary disorders. Infrequently, patients may have more advanced endobronchial involvement that may cause cough, dyspnea, wheezing, endobronchial obstruction, or hemoptysis. Visual identification of KS lesions at endoscopy may be adequate for diagnosis, as the lesions are submucosal, and confirmation by biopsy may be difficult.

Table 1: **Staging Systems for HIV-Associated Kaposi's Sarcoma**

| **New York University System** | | |
|---|---|---|
| Stage | I | Cutaneous, locally indolent |
| | II | Cutaneous, locally aggressive with or without regional lymph node |
| | III | Generalized cutaneous and/or lymph node involvement (more than upper or lower extremities alone; may include minimal gastrointestinal involvement of less than five lesions) |
| | IV | Visceral involvement |
| Subtypes | A | No systemic signs or symptoms |
| | B | Weight loss greater than 10 percent of body weight<br>or<br>Fever greater than 38°C (orally) unrelated to infection and lasting longer than two weeks |

| **University Of California at Los Angeles System** | | |
|---|---|---|
| Stage | I | Limited cutaneous (fewer than 10 lesions or one anatomic area) |
| | II | Disseminated cutaneous (more than 10 lesions or more than one anatomic area)<br>Visceral only (gastrointestinal or lymph nodes) |
| | III | Cutaneous and visceral or pulmonary involvement |
| | IV | |
| Subtypes | I | A and B as above |

| **AIDS Clinical Trials Group System** | | |
|---|---|---|
| | **Good Risk (0)**<br>**(all of the following)** | **Poor Risk (1)**<br>**(any of the following)** |
| Tumour (T) | Confined to skin and/or lymph nodes and/or flat oral lesions confined to the palate | Edema or ulceration<br>Extensive oral KS<br>GI or visceral KS |
| Immune System (I) | CD4 ≥ 200/L | CD4 < 200/L |
| Systemic Illness (S) | No history of opportunistic infection or thrush<br>No "B" symptoms<br>Performance status ≥ 70 (Karnofsky) | History of infection or thrush<br>"B" symptoms<br>Performance status < 70 other<br>Other HIV-related illness |

## Visceral Involvement

Pulmonary parenchymal involvement, an ominous prognostic finding at any stage of the disease, occurs in approximately 10 percent of patients with KS. Radiographic features include unilateral or bilateral mixed interstitial and alveolar infiltrates that may be accompanied by pleural effusions (Plate 9). The pleural fluid is exudative and frequently serosanguineous, and cytologic examination is usually negative for malignant cells. The diagnosis of pulmonary KS may be assumed if infectious causes for the infiltrates have been ruled out, suggestive radiologic signs are present, and extensive endobronchial KS has been seen at bronchoscopy. Only rarely should it be necessary to perform an open lung biopsy to make a diagnosis.

Liver and bone involvement have been reported, but both are unusual. Similarly, symptomatic central nervous system (CNS) disease with mass lesions is quite rare, and investigations to rule out a CNS lymphoma or opportunistic infection should be performed. Pericardial involvement, although rare, may result in the development of a malignant pericardial effusion and tamponade. At autopsy, KS has been found to involve every organ system. Usually, though, involvement of organs other than those discussed above is not associated with KS symptoms during life.

## Clinical Staging

In order to be useful, a staging system should correlate the stage of the disease with response to treatment and overall prognosis. There is still no universally accepted staging system for EKS.

Standard tumour staging systems have not demonstrated good correlation when they have been applied to EKS. There are several reasons for this lack of correlation. The EKS tumour is a multifocal neoplasm that arises simultaneously in multiple sites, and, therefore, the identification of widespread tumour involvement may not have the same implications that it has in a patient with a classical metastasizing cancer. Of perhaps even greater importance is the role played by the underlying immunodeficiency of the EKS patient. It is now well-recognized that more than 50 percent of patients with EKS die as a result of an opportunistic infection or another complication of HIV-induced immunodeficiency and not as a direct result of progressive KS.

Several staging systems for EKS are shown in Table 1. The first system, proposed by the New York University group, arose out of the staging system for classic KS. This system proved to be inadequate for HIV-associated KS, because, with most causes of the disease falling into stages III or IV, the system failed to provide significant prognostic or therapeutic information. For this reason, the University of California at Los Angeles group proposed a second staging system that classified cases according to the bulk of disease present. In this system, significantly longer survival was observed in stages I and III than in stages II and IV. Of even greater importance, though, was the observation that response to treatment correlated most strongly with the presence or absence of systemic symptoms and not with stage.

Recently, the AIDS Clinical Trials Group Oncology Committee proposed a novel three-tiered staging system that classifies EKS based on the extent of the tumours (T), immune system status (I-as assessed by the CD4 cell count), and severity of systemic illnesses (S-based on the presence or absence of opportunistic infections and systemic symptoms and on performance status). This staging system has not yet been evaluated, but it has the potential to be the most useful to the practising clinician, as it incorporates all those aspects of the disease process that must be considered when making treatment decisions for KS patients. Clinicians contemplating future clinical trials should be encouraged to use this system.

# 5. TREATMENT

Owing to the heterogenecity of EKS, it has not been possible to propose simple treatment strategies that encompass all patients. The patients that are most likely to benefit from treatment have not yet been defined.

Response to treatment is not affected by tumour stage, even though the stage of the disease has been found to correlate with survival. In fact, the status of the immune system (as judged by the CD4 count) and the presence of clinical symptoms are significantly stronger determinants both of survival and of response to interferon and chemotherapy. Furthermore, multivariate analysis has shown that these predictors of response are independent of treatment, but no study has demonstrated that treatment of KS has resulted in significant prolongation of life.

Management decisions for patients with KS should be reached only after careful evaluation of all clinical and laboratory parameters. The anticipated benefits and risks of treatment must be carefully balanced with the understanding that the goal of treatment is palliative and not curative. The parameters are displayed in Table 2.

Table 2: **Variables That Must Be Considered When Making Treatment Decisions for Patients with HIV-Associated Kaposi's Sarcoma**

| |
|---|
| **Extent (stage) of Kaposi's sarcoma** |
| **Rate of progression of Kaposi's sarcoma lesions** |
| **Symptoms related to Kaposi's sarcoma lesions** |
| **Presence of opportunistic infection** |
| **Performance status** |
| **Immunologic status** |
| **Hematologic status** |

The extent or bulk of the disease is one of the most important determinants of the need for treatment. Patients with minimal (fewer than five) asymptomatic cutaneous lesions do not need anti-tumour therapy. Such patients should be observed to determine the tempo of the disease, (rate of development of new lesions) and treatment should be withheld unless there is evidence of

1. rapid proliferation,

2. widespread dissemination, or

3. KS-related symptoms.

Patients with slowly growing, low-bulk tumours have the best prognosis within the spectrum EKS. At this stage, KS is a cosmetic rather than a life-threatening problem, and, even though treatment may reduce the number and size of skin lesions, it may not lengthen survival. Because it is usually the development of opportunistic infection rather than progression of KS that results in the death of these patients, treatment should focus on antiviral therapy with zidovudine (AZT) or other similar antiviral agents.

When KS lesions give rise to symptoms, some form of treatment is almost always indicated for palliation.

Once it has been decided that a patient with KS requires treatment, the patient's tolerance for the proposed therapy must be assessed. Patients whose performance status is poor are unlikely to tolerate therapy well and cannot be expected to derive significant survival benefit from treatment. (This consideration applies not only to chemotherapy, but also to interferon, for, to be effective, this medication must be used in moderately high doses that may be associated with debilitating side effects in a significant number of patients.) The presence of active opportunistic infection precludes the use of most chemotherapeutic agents. Furthermore, the neutropenia and thrombocytopenia, which on occasion accompany HIV infection, may make it difficult or impossible to deliver adequate doses of therapy.

## Radiotherapy and Intra-lesion Therapy

The cutaneous lesions of EKS are now known to be as radiosensitive as those of classic KS. Radiotherapy is a local modality and is always undertaken with palliative, not curative, intent. Nonetheless, the importance of this therapeutic tool should not be underestimated. Frequently, radiation may provide significant therapeutic and psychological benefit at a minimal expense in morbidity.

The indications for local radiotherapy are displayed in Table 3. (There is little justification for wide-field treatment of cutaneous lesions in EKS.) Treatment is reserved for lesions that are cosmetically embarrassing on the face (Plate 10) or hands, or for lesions that are painful or ulcerating, in particular those on the feet or in the anorectal or genital areas.

Approximately two-thirds of patients will have a response to radiation. Half of these responses will be complete (the lesion will disappear). In the other half, significant residual pigmentation will remain after treatment (Plate 11), and the radiation itself may result in an area of increased pigmentation. Even so, partial responses usually provide some cosmetic benefit, as the residual lesions are usually flat and may be covered with makeup.

Table 3: **Indications for Local Radiotherapy in HIV-Associated Kaposi's Sarcoma**

| |
|---|
| Cosmesis for lesions on the face, hands, and upper extremities |
| Obstructive lymphadenopathy resulting in regional edema |
| Periorbital edema |
| Lesions on the soles of the feet |
| Anorectal or genital lesions |
| Oral lesions (only if advanced and symptomatic) |
| Ulcerating cutaneous lesions |

Periorbital edema, if left untreated, may progress until the eyelids close completely and functional blindness occurs (Plate 12). This complication of EKS responds promptly to low doses of radiation. Similarly, radiotherapy usually results in good palliation for edema of the lower extremities or genitalia.

As to oropharyngeal lesions, radiation should be reserved for those that are nodular and symptomatic. Treatment of such lesions should be undertaken using fractionated-dose techniques, and care must be taken to provide adequate support for the severe mucositis that may complicate this treatment. Patients should be instructed in the practice of oral hygiene, and mouthwashes and prophylaxis against oral thrush should both be used, as superinfection is common. For patients who have prolonged mucositis, the possibility of a herpetic infection should be considered and appropriate antiviral therapy initiated.

For limited cutaneous involvement and small lesions, local cryotherapy with liquid nitrogen, or intra-lesion therapy with vinblastine may be used. For oral lesions vinblastine may produce a satisfactory result, while avoiding the side effects of radiation.

## Interferon

Although many agents with potentially immunomodulatory activity have been assessed, only the alpha interferons have demonstrated significant activity and acceptable toxicity for the treatment of EKS. Recombinant and nonrecombinant alpha interferons are both active. Complete and partial responses are obtained in approximately one-third of treated patients.

The interferon is administered intramuscularly, initially on a daily basis. In the absence of toxicity, patients that respond to the initial dose remain on maintenance treatment (three times per week).

This level of response is seen only when moderate to high doses of 20 million units or greater are used. At these doses, toxicity requires that treatment be discontinued in approximately 30 percent of patients. The immunomodulatory effects of interferon in this 30 percent patient population have been disappointing; significant improvement in the immune system has not been documented to date.

Interferon has been assessed in combination with both single-agent and combination chemotherapy. Most studies have demonstrated increased toxicity, and no response or survival benefit over either of the treatment modalities used alone.

There is now some suggestion that interferon may have a direct inhibitory effect on HIV replication. *In vitro* data suggest that a synergistic inhibition of viral replication exists when interferon is combined with antiviral therapy such as zidovudine. Clinical trials are currently underway to assess anti-tumour response, antiviral effects, and tolerability of this form of combined modality treatment.

## Chemotherapy

The chemotherapeutic agents that have demonstrated activity in EKS are shown in Table 4. Drugs from the vinca alkaloid family have been used most frequently. Vinblastine is usually started at a dose of 4 to 8 mg IV weekly, and the dose is titrated to maintain a white blood cell count of more than 2.5 X $10^9$/L. At this dose, toxicity is minimal, and approximately one third of patients respond, although less than 10 percent show complete clearing of all lesions. To avoid the myelotoxicity of vinblastine, this drug may be alternated weekly with vincristine 1 mg IV. When the alternating protocol is used, hematologic toxicity is minimal, although neurotoxicity is seen more frequently and may be dose-limiting.

Bleomycin has proven to be a useful agent in the treatment of EKS, as it is one of the few nonmyelosuppressive chemotherapy drugs. It may be used alone or in combination with the vinca alkaloids or other agents and is usually given in a dose of 10 mg/$m^2$ IV weekly. Bleomycin's major toxicities include fever and chills following administration, dermatologic complications, and irreversible pulmonary fibrosis that may be seen following cumulative doses of 200 to 300 mg/$m^2$.

Table 4: **Systemic Treatment for Kaposi's Sarcoma**

| | | |
|---|---|---|
| **Single Agent** | | |
| Interferon | | |
| Chemotherapy | | |
| | Vinca alkaloids: | vincristine<br>vinblastine |
| | Anthracyclines: | doxorubicin<br>epirubicin |
| Epipodophyllotoxins: | etoposide | |
| | | teniposide |
| Others: | | bleomycin |
| **Combinations** | | |
| Chemotherapy | | |
| | Doxorubicin, vincristine, and bleomycin<br>Vincristine alternating with vioblastine<br>Bleomycin and a vinca alkaloid | |
| Interferon and zidovudine (AZT) | | |
| Chemotherapy and AZT | | |

Etoposide and the anthracyclines (doxorubicin and epirubicin) have all demonstrated activity against EKS. These agents may result in a slightly higher overall response rate than the vinca alkaloids, but this response is frequently at the expense of increased marrow suppression and therefore creates a greater risk of infection. Furthermore, all these agents produce alopecia, which frequently is an unacceptable toxic side effect in this patient population.

For patients that have aggressive disease, more intense chemotherapy may be required. The most successful combination to date is a regimen of low-dose doxorubicin (10 or 20 $mg/m^2$), bleomycin (10 $mg/m^2$), and vincristine (2 $mg/m^2$) given intravenously every two weeks. Response is seen in approximately two thirds of patients given this chemotherapy regimen. Opportunistic infection may be slightly higher in patients receiving the higher dose of doxorubicin. It is therefore recommended that the 10 $mg/m^2$ dose be used initially.

# 6. SUMMARY

It must always be remembered that treatment for EKS is palliative in intent and may not contribute significantly to prolongation of survival. It is impossible to make generalized recommendations that will encompass all patients, and treatment decisions must always be individualized after careful consideration of all variables that play a role in determining the eventual outcome of this disease. In the EKS patient population, it is absolutely essential that the risks and toxicity of treatment do not overshadow the expected benefits. Patients should be carefully counselled about the goals of treatment. These goals should be realistic and acceptable to both the patient and the treating physician. The recommendations outlined in Table 5 should be viewed as broad guidelines only.

Table 5: **Guidelines for Treatment of HIV-Associated Kaposi's Sarcoma**

| **Disease Extent** | **Treatment** |
|---|---|
| Minimal KS, no systemic symptoms | Observation or antiviral therapy |
| Minimal KS with systemic symptoms, history of minor or major opportunistic infection or low CD4 count | Antiviral therapy |
| Intermediate mucocutaneous KS | Interferon alone or with antiviral therapy |
| Extensive or rapidly proliferating mucocutaneous KS | Single-agent or combination chemotherapy |
| Visceral KS | Combination chemotherapy |
| Localized symptomatic lesions (pain, bleeding, edema, cosmesis) | Radiotherapy<br>Intra-lesion therapy<br>Cryotherapy |

# 7. SUGGESTED READING LIST

1. R. T. Mitsuyasu, "Kaposi's Sarcoma in the Acquired Immunodeficiency Syndrome," *Infectious Disease Clinics of North America.* Vol. 2 (June 1988):511-523.

2. A. M. Levine and F. Muggia, "Malignancies in the Acquired Immunodeficiency Syndrome," *Current Problems in Cancer.* Vol. 11 (1987):209-255.

3. D. R. Hill, "The Role of Radiotherapy in Epidemic Kaposi's Sarcoma," *Seminars in Oncology.* Vol. 14 (1987):19-22.

4. P. A. Volberding, "The Role of Chemotherapy for Epidemic Kaposi's Sarcoma," *Seminars in Oncology.* Vol. 14 (1987):23-26.

5. S. E. Krown, "The Role of Interferon in the Therapy of Epidemic Kaposi's Sarcoma," *Seminars in Oncology.* Vol. 14 (1987):27-33.