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Kaposi's Sarcoma (KS): HIV/AIDS Related

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Review Article

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Abstract: Studies have been published in the area of Kaposi's sarcoma but much is not known in the area of interaction between HIV and Kaposi sarcoma, etiology, clinical manifestation, staging, immunological mechanism involved, risk factors, diagnostic features and methods, complications involved and treatment. The recent results of Kaposi's sarcoma have been reported in people living with HIV indifferent parts of the world. Cases are unrecognized due inaccurate diagnosis and hence are treated as other diseases. However the most recent studies have shown that Kaposi's sarcoma and HIV coexist together. In Conclusion, Kaposi's sarcoma in HIV is as a result of complex interactions between the host pathogen and the immune mechanisms involved in the protection. Overall, this review has expanded our understanding of the mechanism involved in the pathogenesis and the relationship between tuberculosis and kidney disease. This review will help to improve clinical practices.
Keywords: Kaposi's sarcoma, HIV, Immunity, Cancer.

INTRODUCTION

Kaposi's sarcoma (KS) is a low-grade vascular tumor which is associated with infection with human herpesvirus 8 (HHV-8). It is also known as the KS-associated herpesvirus (KSHV). KS is an endothelial neoplasia that is found typically in cutaneous lesions, whose development stages entail macules, plaques, and nodules. It is the most common malignancy in HIV patients.

ETIOLOGY

AIDS-related KS has several clinical course which ranges from minimal disease presenting as an incidental finding to a rapidly progressing neoplasm that can result in significant morbidity and mortality, depending on the specific sites of involvement [1]. Physical symptoms due to tumors, the psychosocial burden associated with KS are profound and includes emotional distress, guilt, and anger [2].

EPIDEMIOLOGY AND RISK FACTORS

Epidemiologic forms

There are four epidemiologic forms of KS, all of which have been related to infection with HHV-8. These include

- **HIV/AIDS-related or epidemic KS:** AIDS-related or epidemic KS is the most common tumor arising in HIV-infected persons. KS is considered an AIDS-defining illness in the Centers for Disease Control and Prevention (CDC) guidelines. In the United States, KS was over 20,000 times more common in persons with AIDS than in the general population prior to the widespread use of potent antiretroviral therapy (ART), although its incidence has declined substantially since that time [3].
- **Endemic or African:** KS was endemic in all parts of equatorial Africa, particularly in sub-Saharan Africa, prior to the HIV epidemic. Since the onset of the HIV epidemic, the incidence of KS has increased dramatically in Africa [4, 5].
- **Organ transplant-associated:** The incidence of KS is increased after solid organ transplantation, presumably at least partially due to chronic immunosuppression. In addition, the transplant itself may transmit HHV-8 infection. The clinical presentation in this setting is similar to that of classic KS.
- **Classic:** Classic KS is an indolent cutaneous proliferative disease mainly affecting older men of Mediterranean and Jewish origin [6, 7].

Epidemiology of AIDS-related KS

Although KS has been reported among all risk groups for HIV infection, it is most common in homosexual or bisexual men. AIDS-related KS is much less common in heterosexual injection drug users, transfusion recipients, women or children, and hemophiliacs [3]. In patients with AIDS-related KS, the CD4 count appears to be the most important factor associated with the development of KS. In a series of 70

patients who presented with a new diagnosis of KS while on treatment with combined antiretroviral therapy (ART), the rate ratios for developing KS for patients with CD4 counts <200, 200-349, and 350-499 cells/mm3 were 18.9, 3.6, and 4.1, compared to those with ≥500 cells/mm3 [8]. In resource rich areas, AIDS-related KS is predominantly a disease of men. In contrast, in resource poor areas such as sub-Saharan Africa, AIDS-related KS is also more frequent in males, although the difference is less pronounced.

Impact of antiretroviral therapy

Since the introduction of combined antiretroviral therapy (ART), the incidence of KS has declined markedly in HIV-infected patients [9-12]. The standardized incidence ratio (SIR) for KS compared to the general population fell from 22,100 to 3640 with the widespread use of ART. Other large epidemiologic studies have reported a similar decrease in the incidence of KS correlating with the introduction of ART [13]. However, the declining incidence of KS cannot be attributed to a decreased incidence of HHV-8 infection. In one report, the prevalence of HHV-8 infection remained approximately constant among men in San Francisco from 1978/79 (26.5 percent) through 1984/85 (29.6 percent) and 1995/96 (26.4 percent) [14].

Human herpesvirus-8

Studies have reported a strong relationship between the development of KS, HHV-8 infection, and HIV infection [15-17]. In one study conducted in San Francisco, HHV-8 seropositivity was observed in 38 percent of 593 men who have sex with men (MSM) compared to none of 195 heterosexual men [16]. Among HIV-infected patients who were infected with both HIV and HHV-8 at baseline, the 10-year probability of developing KS was approximately 50 percent. The 10-year risk was about 30 percent in HIV-infected men who were not seropositive for HHV-8 at baseline, while there were no cases of KS among the HIV-negative men. This study was conducted before the widespread use of potent combined antiretroviral therapy (ART), and the frequency of progression of HHV-8 infection to KS appears to have decreased since that time.

Steroids and infection

Corticosteroid therapy has been associated with the induction of KS and the exacerbation of preexisting KS in HIV-infected persons, as well as in non-AIDS patients receiving corticosteroids for organ transplantation, autoimmune disorders, or lymphoproliferative diseases [18]. The association of corticosteroids with KS is important because of the frequent use of these agents in HIV-infected patients with a variety of disorders including immune thrombocytopenia (ITP) and Pneumocystis jirovecii pneumonia. In such patients, KS lesions may regress upon reduction or withdrawal of steroids [18, 19].

Another factor is the presence of opportunistic infections which have also been associated with the induction of KS and with the exacerbation of preexisting KS similar to that described with corticosteroid therapy. High levels of proinflammatory cytokines, which have been demonstrated in the setting of opportunistic infections, may account for these effects on KS.

CUTANEOUS KS

Although KS can involve virtually any site in the body, cutaneous disease is most common and is the usual initial presentation for KS.

Clinical manifestations

The cutaneous lesions of KS appear most often on the lower extremities, face (especially the nose), oral mucosa, and genitalia. See picures below showing a). oral mucosa, b). the nose c). the fingers d). of the foot

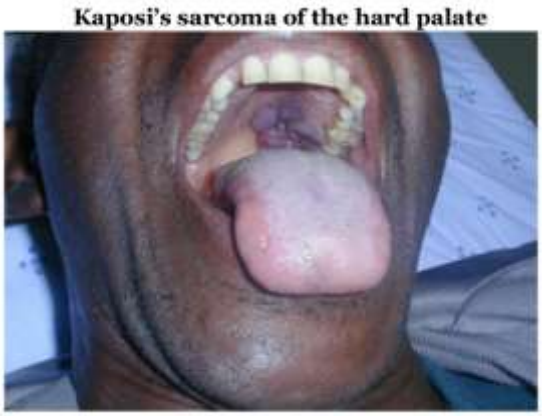

Fig-1: (a) shows oral mucosa KS

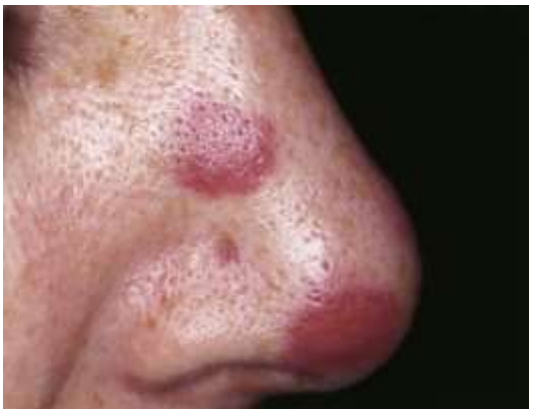

Fig-2: (b) shows KS of the nose

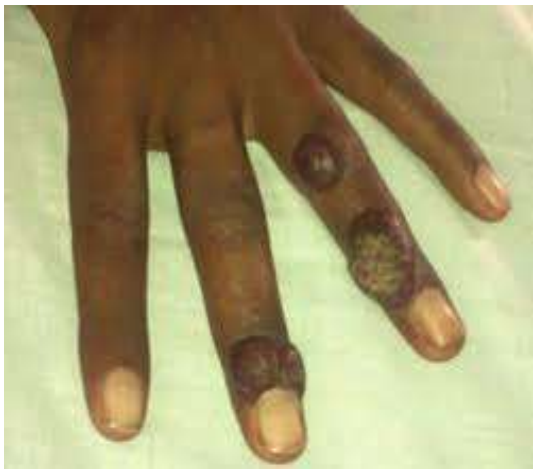

Fig-3: shows KS of the fingers

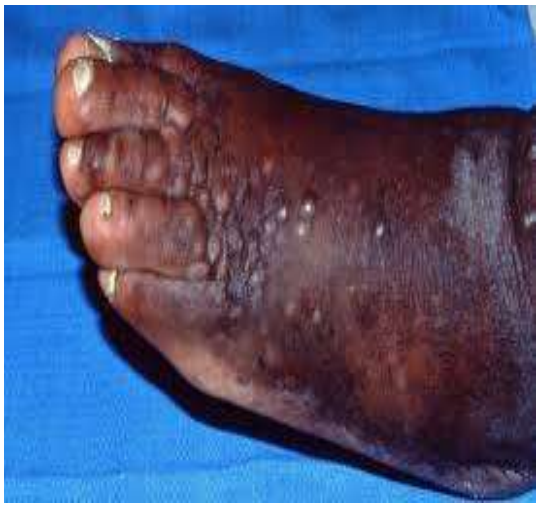

Fig-4: shows KS of the foot

The lesions are often elliptical and may be arranged in a linear fashion along skin tension lines; they may be symmetrically distributed. The lesions are not painful or pruritic and usually do not produce necrosis of overlying skin or underlying structures.

The assortment of colors associated with these lesions is due to their vascularity and includes many hues of pink, red, purple, and brown. Yellow perilesional halos may occasionally be seen. Early lesions can easily be mistaken as purpura, hematomas, angiomas, dermatofibromas, or nevi. More commonly, however, KS lesions are papular, ranging in size from several millimeters to several centimeters in diameter. Less commonly, KS lesions may be plaque-like, especially on the soles of the feet and thigh, or exophytic and fungating with breakdown of overlying skin.

Lymphedema, particularly in the face, genitalia, and lower extremities may be out of proportion to the extent of the disease and may be related to both vascular obstruction by lymphadenopathy and the cytokines involved in the pathogenesis of KS.

Differential diagnosis

A presumptive diagnosis of cutaneous KS can often be made by a trained observer. However, early lesions can easily be mistaken as purpura, hematomas, angiomas, dermatofibromas, or nevi. Bacillary angiomatosis is the most important alternative in the differential diagnosis. Bacillary angiomatosis is caused by Bartonella species, a slow-growing, fastidious, gram-negative bacillus, and is readily treated with antibiotic therapy. Skin lesions of bacillary angiomatosis usually appear as numerous small red to purple papules that may gradually expand into large pedunculated lesions or nodules that may become friable. The rash may be associated with symptoms such as fever, chills, malaise, headache, and anorexia. Biopsy is especially important for atypical lesions that are associated with systemic symptoms or appear or progress rapidly, in order to rule out bacillary angiomatosis. KS and bacillary angiomatosis can occur simultaneously in the same patient. Furthermore, bacillary angiomatosis lesions can be associated with neovascularization and solid areas of spindle cells that mimic KS. The diagnosis of bacillary angiomatosis is established by the identified of the causative organisms with Warthin-Starry silver staining. Less commonly, KS can be mimicked by extrapulmonary Pneumocystis jirovecii, even in the absence of coexisting lung infection [20].

Diagnosis

Although a presumptive diagnosis of KS can often be made based upon the characteristic appearance of the lesions, this should be confirmed by a biopsy whenever possible. Biopsy is especially important for atypical lesions that are associated with systemic symptoms or appear or progress rapidly, in order to rule out bacillary angiomatosis.

Pathology

There are three histologic features that are characteristic of KS, both in cutaneous and visceral sites: angiogenesis, inflammation, and proliferation. The lesions generally show two major abnormalities: whorls of spindle-shaped cells with leukocytic infiltration and neovascularization with aberrant proliferation of small vessels.

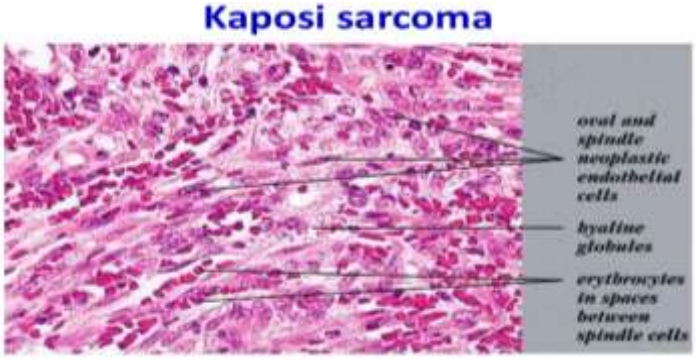

Fig-5: shows Histological characteristics of KS

These small vessels lack a basement membrane and display leaky behavior with microhemorrhages and hemosiderin deposition [21]. As the disease progresses, it evolves from patches to plaques, and then to a nodular form. The characteristic histologic pattern of KS does not differ among the affected epidemiologic groups. It poses problems in histologic diagnosis due to its broad morphologic spectrum and mimicry of many benign vasoproliferative lesions and tumors with a prominent spindle component [22]. Distinguishing KS from other benign or malignant vascular tumors, as well as other nonvascular spindle cell soft tissue neoplasms, can be challenging [23-26]. Early-stage KS represents a reactive lesion that can either regress or progress.

Progression is related to the long-lasting expression of HHV8 latency genes in KS lesions, including latent nuclear antigen-1 (LANA-1) [21], cyclin-D1[27,28], and bcl-2 [29]. HHV8-related induction of the receptor tyrosine kinase c-kit was shown by gene expression profiling in cultured endothelial cells to play a key role in KS tumorigenesis.

VISCERAL DISEASE

KS involvement has been observed in almost all visceral sites, including lymph nodes, liver, pancreas, heart, the testes, bone marrow, bone, and skeletal muscle [30,31]. The most frequent sites of no cutaneous disease are the oral cavity, gastrointestinal tract, and respiratory system. However, visceral involvement as the initial manifestation of KS is relatively uncommon.

Oral cavity

Involvement of the oral cavity occurs in about one-third of patients with KS and is the initial site in about 15 percent. The dental practitioner is often the first to identify these lesions. The diagnosis of KS should be confirmed by biopsy whenever possible.

The intraoral site most commonly affected is the palate followed by the gingiva [32]. Intraoral lesions may become easily traumatized during normal chewing, which can result in pain, bleeding, ulceration, or secondary infection. If lesions are advanced, they may interfere with nutrition and speech. The presence or absence of symptoms from oral lesions is often a major factor in treatment decisions.

Gastrointestinal tract

Prior to the widespread introduction of ART, the gastrointestinal tract was involved in approximately 40 percent of patients with KS at initial diagnosis and in up to 80 percent at autopsy. Gastrointestinal involvement can occur in the absence of cutaneous disease. Gastrointestinal lesions may be asymptomatic or may cause weight loss, abdominal pain, nausea and vomiting, upper or lower gastrointestinal bleeding, malabsorption, intestinal obstruction, and/or diarrhea [33, 34]. Gastrointestinal KS lesions are easily recognized by the endoscopist [35].

They are typically hemorrhagic nodules that can be either isolated or confluent and may occur in any portion of the gastrointestinal tract [36]. See picture below.

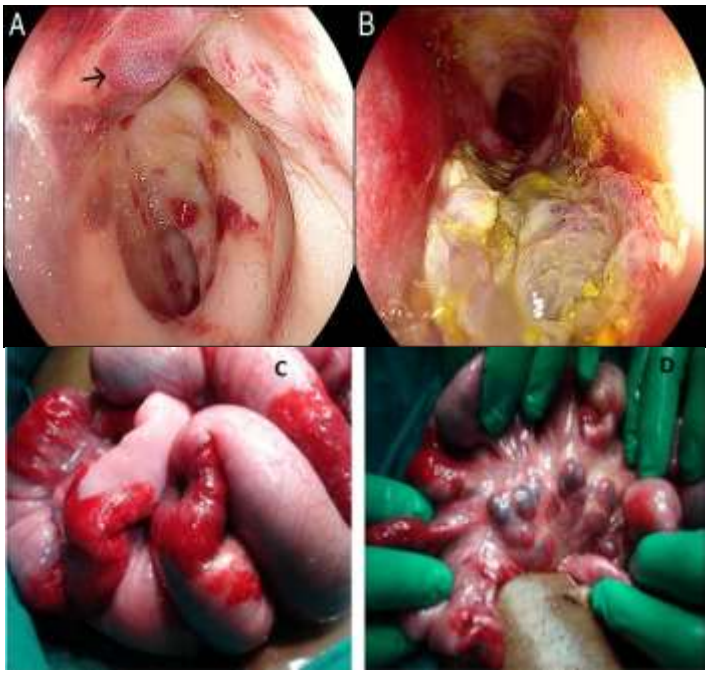

Fig-6: (A,B,C &D) shows Gastrointestinal KS lesions

The diagnosis of KS should be confirmed by biopsy whenever possible, although biopsies may not demonstrate KS because the lesions tend to be submucosal. High grade lesions are more likely to be associated with invasion and dissemination. Treatment is usually dictated by the presence or absence of symptoms.

Respiratory system

Pulmonary involvement is common in AIDS-related KS. Affected patients can present with shortness of breath, fever, cough, hemoptysis, or chest pain, or pulmonary involvement may be an asymptomatic finding first observed on chest x-ray. Radiographic findings are variable and can include nodular, interstitial and/or alveolar infiltrates, pleural effusion, hilar and/or mediastinal adenopathy, or even an isolated nodule. The KS lesions have a characteristic appearance of cherry-red, slightly raised lesions seen at bronchoscopy, which can result in a presumptive diagnosis of pulmonary KS. Although bronchoscopic and radiographic findings correlate quite well, patients who have KS documented by bronchoscopy may on occasion have normal chest x-rays.

Treatment decisions are usually guided by the presence of respiratory symptoms, the extent of radiographic and bronchoscopic disease, and exclusion of a concomitant pulmonary infection as the cause of the clinical findings.

STAGING AND EVALUATION

Staging system

The most commonly utilized staging system for AIDS-related KS was developed by the AIDS Clinical Trial Group (ACTG) of the National Institute of Health [37]. This system divides patients into good or poor risk prognostic categories, taking into account both the KS and HIV infection.

Patients are categorized according to three parameters

- **Extent of tumor (T):** a favorable prognosis (T0) is associated with disease limited to the skin or with

minimal involvement of the oral cavity. Those with associated lymphedema, more extensive oral cavity involvement, or other visceral disease are considered to have a poor prognosis (T1).

- **Immune status (I):** the degree of immunosuppression from the HIV infection is an important prognostic factor. Patients with a CD4 count greater than 200 cells/microL are considered to have a favorable prognosis (I0) while those with a lower CD4 count have classified as poor prognosis (I1).
- **Severity of systemic illness (S):** Features associated with a poor risk included the following (S1): a history of opportunistic infection, thrush, B symptoms (fever, night sweats, significant weight loss, and diarrhea for more than two weeks). Patients without any of these factors have a more favorable prognosis (S0).
- The overall patient assessment requires that good-risk patients have a favorable prognosis according to all three parameters. This was illustrated by an analysis of 144 patients with KS prospectively included in the Swiss HIV Cohort Study [38].

Initial evaluation

The initial evaluation of a patient with KS consists of a thorough physical examination with special attention paid to those areas typically affected by the disease, such as the lower extremities, face, oral mucosa, genitalia, gastrointestinal tract, and lungs. Evaluation for visceral involvement is guided by symptomatology and basic laboratory testing.

Testing the stool for occult blood is the simplest way to screen for gastrointestinal involvement. Endoscopy is usually reserved for patients who test positive for occult blood or have gastrointestinal symptoms. Chest x-ray is useful to screen for pulmonary lesions. Bronchoscopy should be reserved for those with an abnormal radiograph and persistent respiratory symptoms in the absence of another cause. CT scanning of the chest, abdomen, and pelvis is typically not necessary. The CD4 cell count and HIV viral load are important for staging and prognosis, and thus may be useful in making treatment decisions.

TREATMENT

The major goals of treatment are symptom palliation, prevention of disease progression, and shrinkage of tumor to alleviate edema, organ compromise, and psychological stress [39]. Systemic treatment with potent combination antiretroviral therapy (ART) is recommended for virtually all patients with AIDS-related KS [40-41]. The need for treatment beyond ART and the choice among the various options depend upon the extent of disease, the rapidity of tumor growth, the HIV-1 viral load, the CD4 cell count, and the patient's overall medical condition [42]. Locally directed therapy is often used to palliate symptoms caused by a specific tumor or to treat cosmetic disfigurement. Systemic therapy is used for more extensive disease but injury to an immune system that is already severely compromised should be avoided whenever possible.

Combined antiretroviral therapy

Combination ART is recommended for virtually all patients with AIDS-related KS, and may be the only therapy required in the absence of specific indications for chemotherapy.

The introduction of ART has been associated with a substantial decrease in both the incidence and severity of newly diagnosed KS in HIV infected patients. A French database study that included 54,999 patients with over 180,000 patient years of follow-up found that the incidence rate for new cases of KS fell from 32 per 1000 person-years in 1993-1994 to 3 per 1000 person-years after 1999 [9]. Furthermore, the incidence of visceral involvement at presentation fell from more than 50 percent to less than 30 percent. Similar dramatic decreases have been seen in other studies [43, 44]. Observational studies indicate that the natural history of AIDS-related KS has changed since the introduction of ART in addition to a decrease in the KS incidence [45]. A retrospective study that analyzed KS cases from a database of 4439 persons with HIV infection both before ART (1990 to 1996) and after ART (1997 to 2002) found that the mean CD4 count and the mean HIV RNA levels were similar in the 366 patients from the pre-ART era and in the 40 patients in the post-ART era [46]. However, the overall risk of dying was significantly lower in the post-ART era (hazard ratio, 0.24).

Immune reconstitution due to control of the HIV infection is the most likely explanation for this altered prognosis rather than a direct effect on tumor. Although HIV protease inhibitors have antiangiogenic properties and block the development and progression of KS-like lesions in nude mice [47], there was no difference in the likelihood of clinical response associated with the use of these agents [48]. Additionally, a decrease in incidence of KS has been observed with ART regimens that do not contain protease inhibitors [9].

Although treatment with ART causes increases in CD4 counts above the levels typically associated with increased susceptibility to infection, some patients develop HIV-related KS despite apparent correction of their immunodeficiency [49].

Immune reconstitution inflammatory syndrome

The term "immune reconstitution inflammatory syndrome" (IRIS) is used to describe a collection of host responses that can occur following the initiation of ART. In addition to worsening of symptoms from preexisting infections with IRIS, the initiation of ART has been associated with progression of KS within three to six weeks after starting antiretroviral therapy [50,51].

The relationship between IRIS and KS is illustrated by two reports:

In one series of 150 therapy-naive patients who presented with KS, 10 (7 percent) developed progressive KS when ART was initiated [50]. The risk of IRIS appeared to be increased in those with a higher CD4 count or KS-associated edema. Despite the progression of KS, continuation of ART was possible in these patients.

In another series of nine cases from a single institution, the progression of KS occurred at a mean of five weeks after initiation of ART and was associated with a rising CD4 count and a decreasing viral load [51]. In all patients in whom systemic chemotherapy was used, tumor regression was observed, and discontinuation of ART was not required.

Local symptomatic therapy

Local treatment modalities are useful for cosmesis or the management of symptomatic bulky KS lesions, but they do not prevent the development of new lesions in untreated areas. The most widely used local treatment approaches include:

- **Intralesional chemotherapy**

  Intralesional chemotherapy can induce regression of injected tumors and is preferred for small lesions. Vinblastine is the most widely used agent. It can be injected directly into a KS lesion as a 0.2 to 0.3 mg/mL solution with a volume of 0.1 mL per 0.5 cm 2 of lesion. Multiple injections may be necessary for larger lesions. A second series of injections is often necessary three to four weeks later. Treated lesions will fade and regress although typically not resolve completely [52-54].

- **Radiation therapy**

  The primary role of radiation therapy is to treat symptomatic disease that is too extensive to be treated with intralesional chemotherapy, but is not extensive enough to require systemic therapy. Although discomfort from radiotherapy is frequent, it usually resolves within two weeks of treatment. Radiation therapy does not have a role in patients with extensive KS, as was illustrated by a randomized trial from Zimbabwe [55].

- **Topical alitretinoin**

  Alitretinoin (9-cis retinoic acid) is available as a topical gel that the patient can apply to treat cutaneous KS lesions. This agent is rarely used, since the topical gel can cause inflammation and lead to pigmentation changes in dark-skinned patients. In two phase III studies involving 402 patients, alitretinoin was associated with a shorter time to response, a longer duration of response, and a longer time to disease progression compared to a placebo vehicle gel [23, 24]. In these trials, responses were seen in 35 and 37 percent of patients after 12 weeks of treatment, compared to 7 and 18 percent with placebo. Responses were seen in patients with a wide range of baseline CD4+ lymphocyte counts.

- **Systemic chemotherapy**

  Systemic chemotherapy is generally used for patients with more advanced KS or when there is evidence of rapid disease progression [6]. When chemotherapy is indicated, treatment with pegylated liposomal doxorubicin or liposomal daunorubicin is generally recommended as the first-line treatment for KS [6]. Other agents that have been used include paclitaxel, bleomycin , vinblastine , vincristine , and etoposide [25-27].

  Generally accepted indications for adding systemic chemotherapy to ART include:

  - Widespread skin involvement (eg, more than 25 lesions)
  - Extensive cutaneous KS that is unresponsive to local treatment
  - Extensive edema
  - Symptomatic visceral involvement
  - Immune reconstitution inflammatory syndrome (IRIS)

- **Liposomal anthracyclines**

  Treatment with pegylated liposomal doxorubicin or liposomal daunorubicin is generally recommended as the first-line treatment for AIDS-related KS when systemic chemotherapy is indicated [56]. Pegylated anthracyclines have a longer plasma half-life than nonliposomal formulations. Liposomal formulations have less toxicity in nontarget organs than conventional anthracyclines and provide the theoretical advantage of higher tumor concentrations of drug.

  Liposomal anthracyclines can reliably shrink tumors, lessen edema, and cause the color of lesions to fade. Response rates range from 30 to 60 percent depending upon the definition of clinical response and the specifics of the various trials. In randomized multicenter trials, each of these agents was as effective as or superior to conventional combination chemotherapy (bleomycin and vincristine with or without nonliposomal doxorubicin) in terms of response rates and had a better toxicity profile [57-59]:

  In one trial, 258 patients were randomly assigned to pegylated liposomal doxorubicin (20 mg/m 2 every three weeks) or a combination regimen of doxorubicin, bleomycin, and vincristine [60]. The response rate (virtually all responses were partial) was significantly higher with pegylated liposomal doxorubicin (46 versus 25 percent), which was also associated with less toxicity. Similar findings were

noted in another trial of 241 patients (59 versus 23 percent response rate) [61- 63]. Both clinical benefit and tumor responses were more frequent with liposomal doxorubicin.

Side effects from these liposomal products are in general mild. In particular, alopecia and neuropathies are unusual with these preparations, in contrast to the side effect profile of conventional combination chemotherapy regimens. The diminished cardiotoxicity with liposomal anthracyclines permits higher cumulative doses of anthracycline to be administered, lengthening the duration over which these agents may be used [64].

The potential for prolonged control of KS was illustrated by a study of 98 patients treated with ART plus pegylated liposomal doxorubicin between 1997 and 2002 [65]. At a median follow-up of 29 months, 29 patients (30 percent) had died, including three with progressive KS. Among the 61 patients who had a complete or partial response of their KS, only eight (13 percent) relapsed after completing chemotherapy. The optimal duration of therapy with liposomal anthracyline is uncertain. A course of four to six cycles of liposomal doxorubicin followed by a period of observation may be reasonable.

- **Taxanes**

Although paclitaxel is potentially more toxic than the liposomal anthracyclines, it has striking efficacy as a second-line treatment for KS [66-70], and may be an alternative for initial therapy of patients with advanced, symptomatic KS.

The efficacy of paclitaxel was originally demonstrated in a phase II study in 28 evaluable patients, in which 20 (71 percent) had major responses to a regimen of 135 mg/m 2 every three weeks. Responses were noted in all five patients with pulmonary KS and all four who had previously received anthracycline therapy.Toxicity included grade 4 thrombocytopenia in 6 of 29, and grade 4 neutropenia in 22 of 29 patients treated without hematopoietic growth factors.Paclitaxel (100 mg/m 2 every two weeks) was compared with pegylated liposomal doxorubicin (20 mg/m 2 every three weeks) in a randomized trial conducted after the introduction of routine treatment with ART [71]. Paclitaxel is metabolized through the cytochrome P450 enzymes, as are many of the antiretroviral drugs. Profound paclitaxel-related toxicity has been ascribed to an interaction between this drug and antiretroviral drugs in at least two patients [72]. However, others have failed to document alterations in paclitaxel elimination pharmacokinetics in one patient treated concurrently with indinavir, ritonavir , saquinavir , and nevirapine [73]. Caution is urged when co-administering these agents.

- **Steroids**

Corticosteroid therapy has been associated with the induction of KS and with the exacerbation of preexisting KS in HIV-infected persons, as well as in non-AIDS patients receiving corticosteroids for organ transplantation, autoimmune disorders, or lymphoproliferative diseases [74]. The association of corticosteroids with KS is important because of the frequent use of these agents in HIV-infected patients with a variety of disorders including immune thrombocytopenic purpura and Pneumocystis jirovecii pneumonia. In patients being treated with steroids, KS lesions may regress upon reduction or withdrawal of steroids [75,76].

Other agents

A number of other agents have been studied in a more limited way in patients with AIDS-related KS, and these may have utility as second line therapy:

Vinorelbine

Vinorelbine may be effective in the treatment of patients with AIDS-related KS who have failed other treatments, including other vinca alkaloids. In one series of 35 patients treated with vinorelbine (30 mg/m 2 every two weeks), three (9 percent) had a complete clinical response, and 12 (34 percent) had a partial response, which lasted for a median of 151 days [77].

Etoposide

Oral etoposide has been reported to have activity in AIDS-related KS when given either in fractionated doses (20 mg/m 2 every eight hours for 7 of 21 days) [78] or as a once daily dose of 50 mg for 7 of every 21 days [79].

Interferon-alfa

Interferon-alfa (IFNa) is a biologic response modifier that produces clinically significant responses in approximately 20 to 40 percent of patients with AIDS-related KS, especially those with disease limited to the skin and relatively modest immunosuppression [80,81]. However, IFNa is rarely used because of the availability of other agents with a more favorable benefit-to-risk ratio.

In a randomized trial, patients with AIDS-related KS were treated with zidovudine and IFNa at a dose of either one or eight million units subcutaneously per day [82]. With the high-dose regimen, the response rate was much higher (31 versus 8 percent) and the median time to progression longer (18 versus 13 weeks). Responses at both doses were more likely in patients with CD4 counts above 150/microL. However, almost all patients in the high-dose arm required dose reduction for significant toxicity consisting of fever, chills, rigors, neutropenia, hepatotoxicity, and cognitive impairment.

Experimental approaches

Recent advances in the understanding of the pathogenesis of KS are uncovering potential targets for KS therapies[83,84]. Such targets include angiogenesis, sex hormones, vitamin D and its analogs, and cellular differentiation.

Imatinib

Imatinib is an orally active tyrosine kinase inhibitor that has demonstrated activity in AIDS-related cutaneous KS. In a pilot series, five of ten men with progressive disease despite chemotherapy and/or ART had an objective partial response to imatinib (300 mg twice daily) [85]. A larger trial has been completed by the NIH/National Cancer Institute; final results are not yet available. Activation of the platelet-derived growth factor and c-kit receptors (both receptor tyrosine kinases) are important in the growth of KS lesions and imatinib inhibits both of these receptors.

Inhibitors of mTOR pathway

Rapamycin and temsirolimus are inhibitors of the mTOR pathway and appear to have activity in patients with KS. The demonstration of patients who had regression of their transplant-related KS when treated with rapamycin indicates that the PI3K/AKT/mTOR pathway may be important in the pathogenesis of KS [86]. In another study, seven patients with HIV-related KS were treated with a combination of rapamycin plus antiretroviral therapy [87]. Three patients, all on protease inhibitor containing regimens, had a partial response of their KS to treatment.

Bevacizumab

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor, which contributes to the pathogenesis of KS. In a phase II study, treatment of 17 patients with HIV associated KS using bevacizumab resulted in objective responses (complete or partial) in five cases and stable disease in nine additional cases [88]. Additional studies will be required to determine the role of bevacizumab in these patients.

Vitamin D and its analogs Primary KS tumors and cell lines derived from KS lesions express high levels of the vitamin D receptor. In one report, treatment with 1, 25 dihydroxyvitamin D3 inhibited the growth of KS cells in vitro and in xenograft models [89].

Miscellaneous agents

A number of other agents have shown at least some evidence of activity in early studies in patients with AIDS-related KS. These include the angiogenesis inhibitors fumagillin [90] and thalidomide [91], the differentiation-inducing agent 9-cis retinoic acid [92], the matrix metalloproteinase inhibitor COL-3 [93], interleukin-12 [94,95], and intralesional injection of human chorionic gonadotropin) [96, 97].

Anti-HHV-8 therapy

Identification of HHV-8 as the etiologic agent of KS provides another potential target for treatment. However, there are no specific anti-HHV-8 therapies available.

Case-control studies of historical cohorts of HIV-seropositive subjects suggest that there is a lower incidence of KS in patients treated with ganciclovir or foscarnet, but not acyclovir [98, 99]. Indirect evidence for the efficacy of ganciclovir also comes from a randomized trial in which 377 HIV-seropositive patients with cytomegalovirus retinitis were assigned to receive a ganciclovir intraocular implant plus oral ganciclovir, a ganciclovir implant plus oral placebo, or intravenous ganciclovir alone [100]. Treatment with oral or intravenous ganciclovir reduced the risk of KS by 75 and 93 percent, respectively, compared with placebo. New agents might inhibit the specific protein products of the virus that contribute to KS spindle cell growth as well as block the effects of the switched-on chemokine receptor. As this work progresses, the primary focus will be to sustain a high level of cellular immunity with antiretroviral therapy so that host defenses can provide the needed surveillance to suppress the neoplasm.

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