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Int J STD AIDS 2009 20: 410

DOI: 10.1258/ijsa.2008.008353

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Presentation and survival of patients with AIDS-related Kaposi's sarcoma in Jos, Nigeria

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Summary: AIDS-related Kaposi's sarcoma (AIDS-KS) remains a significant cause of morbidity and mortality. We describe the pattern of presentation and survival in Jos, Nigeria. We identified 48 HIV-positive patients with AIDS-KS and matched them for age and sex with an equal number of HIV-positive patients without AIDS-KS. We compared their clinical, immunological, virological characteristics and survival. They were similar in age and body mass index profile but patients with AIDS-KS had more tuberculosis co-infection ($P, 0.02$), lower median CD4 count ($P, 0.003$) and higher mortality ($P, 0.002$). Surprisingly, patients with AIDS-KS had lower levels of median viral load (29,347 copies/mL) compared with controls (80,533 copies/mL). We recommend specific AIDS-KS therapy in addition to highly active antiretroviral therapy in order to improve survival.

Keywords: AIDS-related Kaposi's sarcoma, survival, Nigeria

INTRODUCTION

When the Hungarian dermatologist Moriz Kaposi originally described Kaposi's sarcoma (KS) in 1872, it was reported mainly in elderly men from eastern European and Mediterranean countries (classic form). Since that initial description, three additional forms have been described: Endemic KS is prevalent in central Africa, primarily affecting young men with aggressive skin and visceral lesions. Transplant-related KS has been reported in patients with renal transplants on immunosuppressive therapy and most recently epidemic KS, better known as AIDS-related KS (AID-KS).¹

AIDS-KS was first reported in homosexual men with acute cell-mediated immunodeficiency in 1981. It was one of the first conditions recognized as an opportunistic sequela of HIV infection, and remains the most common AIDS-associated neoplasm.² The epidemiology of AIDS-KS has long suggested that an environmental or infectious sexually transmitted cofactor might contribute to the development of KS. The search for such a co-factor led, in 1994, to the discovery of a novel herpes virus, human herpes virus-8 (HHV-8), also known as the KS-associated herpes virus (KSHV). HHV-8/KSHV is found in all forms of KS, and infection with the virus appears to be necessary but not sufficient for KS to develop.³

In the United States, KS incidence in white men prior to the AIDS epidemic was 0.3 per 100,000 population in 1973–1978, but rose to a high of 8.9 per 100,000 population between 1989

and 1991. After the onset of the AIDS epidemic, 90% of people with KS were aged 20–54, whereas individuals in that same age range comprised only 11% of KS cases in 1973–1978.⁴ Contrary to the experience in the United States, the incidence of KS in HIV-infected individuals is increasing in sub-Saharan Africa, where there is limited access to antiretroviral therapy (ART). Although KS was endemic in central and east Africa before AIDS, AIDS-KS has become the most frequently diagnosed tumour in several African countries.^{5,6} In Uganda, age-standardized incidence rates rose from 3.2 in men and 0.1 in women per 100,000 in 1960–1966 to 39.3 and 21.8 per 100,000, respectively, in 1995–1997, and KS accounted for 2% of childhood tumours in the 1960s and 33% in the 1990s. At the same time, the male-to-female ratio of KS incidence in adults declined from 20:1 to 2:1.⁷ KS in HIV-infected people has been associated with a higher socioeconomic status, a history of sexually transmitted diseases and a higher number of sexual partners.^{8,9}

The precise incidence of AIDS-KS and the clinical presentations vary markedly across the African continent. Globally, the highest incidence is recorded in tropical Africa, with a narrow belt stretching westward across the Congo to the coast of Cameroon and southward down the rift valley into Malawi and parts of South Africa.^{10,11} All forms of KS are more common among men than among women. In the absence of immunosuppression, KS is currently estimated to be 3–4 times more common in men, but even higher male-to-female ratios have been reported for the classic and African endemic forms of the disease. KS has also been reported to behave more aggressively in HIV-infected women than in men.^{12,13} KS can manifest at any time in the course of HIV infection, but becomes more common as immunocompetence declines. Its distribution, rate of progression and secondary complications vary tremendously.

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Although the incidence of AIDS-KS is reported to have fallen by more than 90% in some populations with the introduction of highly active antiretroviral therapy (HAART) and safe sexual practices, the situation may be the reverse in most of Africa due not only to a more rapid rate of progression of HIV disease but also to the unavailability of HAART in most communities. We wanted to describe the pattern of AIDS-KS in adult Nigerians presenting to an antiretroviral treatment programme in Jos, Nigeria and to compare survival in HIV-infected patients with and without AIDS-KS.

PATIENTS AND METHODS

The Jos University Teaching Hospital HIV cohort is the largest single-centre cohort in Nigeria. We prospectively collect data on all individuals enrolled for care. HIV-1-infected patients are seen at regular intervals for clinical assessment, follow-up and laboratory monitoring. This study focused on patients presenting at our centre with features of AIDS-KS from July 2004 to June 2005. For each patient with AIDS-KS, one age- and sex-matched HIV-positive patient without AIDS-KS was selected as a control. Demographic data were obtained as well as a history of significant co-morbidities. Body mass index (BMI) was calculated using the measured weights (kg) and heights (m²) and BMI was grouped according to the WHO classification.

Detailed clinical evaluation was done to characterize type and distribution of lesions in patients with AIDS-KS. Clinical staging was also carried out using the ACTG system. HIV-1 infection was confirmed using the Western blot assay (Immunetics, Inc, Boston, MA, USA). Diagnosis of Kaposi’s sarcoma was made on the basis of clinical parameters and by histological confirmation. CD4+ count was measured by flow cytometry (Cyflow, Partec, Munster, Germany) and expressed as cells/mm³. Plasma HIV-1 RNA levels were measured using the Roche-Ampiclor HIV-1 monitor test, version 1.5 (Roche-Ampiclor®-Roche Diagnostics, Branchburg, NJ, USA). The viral load ≤400 copies/mL of plasma was considered undetectable. All patients who qualified for HAART according to national guidelines were commenced on therapy and those with opportunistic infections were also treated. Follow-up was for 12 months with documentation of outcome at the end of the observation period.

Statistical analysis

Statistical analysis was performed using the Epi info software, version 3.3.2 (CDC, Atlanta, GA, USA) and SPSS version 16.0. The results are reported as means ± SD. Univariate and multivariate analysis was used to correlate the extent of disease with immunologic and virologic parameters. The Kaplan–Meier survival plot with log-rank statistic was used to compare the survival between patients who had AIDS-KS and those without AIDS-KS. *P* value <0.05 was considered statistically significant.

RESULTS

Clinical information was available on a total of 2888 HIV-positive patients at the end of the observation period. A total of 96 patients were recruited. Forty-eight of them had AIDS-KS, whereas 48 were HIV-positive controls without AIDS-KS (Table 1). The 48 patients presenting with AIDS-KS represent 1.6% of the total adult patients enrolled for HIV care at that time. The mean age

Table 1 Characteristics of HIV-positive patients with and without AIDS-KS in Jos, Nigeria

Parameter	AKS (n = 48)	Control (n = 48)	P value
Sex (Male %)	41.6	43.7	0.83
Age (years)	36 ± 8	36 ± 7	0.74
BMI (kg/m ²)	20.9 ± 4.3	22.1 ± 3.9	0.10
HAART use (%)	19.1	25	0.46
Duration of HAART use (months)	15.7 ± 10.3	15.1 ± 7.8	0.40
Tuberculosis (%)	54.2	33.3	0.02
Median baseline CD4 (cells/mm ³)	96	126	0.003
Median baseline HIV RNA (copies/mL)	29,347	80,533	0.09

BMI = body mass index; AIDS-KS= AIDS-related Kaposi’s sarcoma; HAART= highly active antiretroviral therapy

was 36 ± 8 years (median: 35 years) for the AIDS-KS and 36 ± 7 years (median: 34 years) for the control group. There were 28 women and 20 men with AIDS-KS and 27 women and 21 men without AIDS-KS. The mean BMI was 20.9 ± 4.3 and 22.1 ± 3.9 for the AIDS-KS and the control groups, respectively. The median CD4 counts were 96 cells/mm³ (2–306) and 126 cells/mm³ (9–743) for the study and control groups, respectively. The median HIV RNA copies/mL of plasma was 29,347 (200–1,038,317) and 80,533 (200–446,020) for the study and control groups, respectively. Nine (19.1%) of the AIDS-KS group had a positive history of HAART use with a mean duration of use being 15 ± 10 (months) while 12 (25%) of the control group were on HAART (mean duration was 15 ± 7 months) at the time of enrolment. Twenty-six (54.2%) of those with AIDS-KS had tuberculosis (TB) as a co-morbid illness while 16 (33.3%) of the control group also had TB.

The men-to-women ratio of AIDS-KS was 1:1.4. Thirty-seven (77.1%) in the study group had disseminated disease while 11 (22.9%) had localized disease (Table 2). Twelve subjects (25%) had mainly plaques, 15 (31.2%) had nodules, while 21(43.8%) had a combination of plaques and nodules. Twenty-six (54.1%) patients with AIDS-KS presented with lesions on the limbs. Only two (4%) of them accessed cytotoxic therapy. One year mortality was 22.9% (11 subjects) in those with AIDS-KS while none had died in the control group. Apart from those who died, all study patients and controls were available for the 12 months of observation. Survival probability statistics (log-rank and Wilcoxon tests with Kaplan–Meier plot) revealed

Table 2 Characteristics of HIV-positive patients with AIDS-KS in Jos, Nigeria

Parameter	n	Frequency (%)
Sex distribution		
Male	20	41.7
Female	28	58.3
Distribution of lesions		
Localized	11	22.9
Generalized	37	77.1
Type of lesion		
Plaques	12	25
Nodules	15	31.2
Combined	21	43.8

Generalized KS: T1S1, Localized KS: T0S0²²
AIDS-KS = AIDS-related Kaposi’s sarcoma

a statistically significant difference in mortality between the two groups (Figure 1).

DISCUSSION

The prevalence of AIDS-KS in our setting is 1.6% of the total patient population accessing ART in our facility. Rates between 5% and 10% were reported at the height of the epidemic in the USA. With the introduction of HAART, the rates dropped drastically to less than 1% in parts of the same country that were worst hit by HIV.¹⁴ The annual incidence of AIDS-KS was also reported to have reduced by 39% between 1994 and 2003 following the introduction of HAART in a pan-European multicentre study.¹⁵ AIDS-KS has also been reported to be highly prevalent in Mozambique, a country that has one of the highest prevalence of HIV in the world. Our values differ significantly from that of Thailand where a prevalence of less than 0.2% has been reported despite the HIV epidemic.

Prior to the HIV epidemic, KS was reportedly more common in men than in women, with a sex ratio of >10:1. We found a different picture with women presenting more frequently with the disease, at a ratio of 1:1.4 (male to female). In a recent report from mid-western Nigeria, a male:female ratio of 1.6:1 was observed in a cohort of HIV-infected patients.¹⁶ This change in pattern may be attributed to the fact that the HIV epidemic is affecting an increasingly higher number of women in sub-Saharan Africa with over 60% of persons living with the virus in this region being women. The same trend has also been reported from Kenya.^{17,18}

Unlike the classic form of KS that affects mainly middle-aged men, AIDS-KS tends to occur at a much younger age. The median age at presentation in our cohort was 35 years. This is in keeping with reports from other parts of Nigeria and the rest of the world where AKS has been found to occur more frequently at a younger median age.^{4,10,13,16} This change in age of incidence

may be explained by the fact that HIV is reported to be most prevalent among those aged 20–49 years in sub-Saharan Africa, coupled with high-risk behaviour and immunosuppression.

The degree of immunosuppression was significantly higher in patients with AIDS-KS than in those without AIDS-KS. Baseline HIV RNA levels were also higher in the study group. HIV contributes to the pathogenesis of KS by inducing the immunosuppression necessary for the clinical expression of disease. In addition, the HIV tat protein induces a number of cytokines known to promote HIV replication, while also inducing KS cell growth, invasion and angiogenesis.¹⁹

A higher percentage of those without AIDS-KS had had access to ARV's than those who had the disease (25% versus 19.1%). ART is associated with significant improvement in the survival of patients with KS, and has become an essential component of KS management. Prior to the availability of effective ART, 90% of patients with pulmonary KS progressed and died of their disease. In contrast, where effective ART is available, the proportion of patients with pulmonary KS experiencing fatal disease progression has been reduced to 47%. In multivariate analyses, the Multicenter AIDS Cohort Study demonstrated an 81% reduced risk of death for KS patients treated with combination ART.²⁰ Co-existing opportunistic infections, mainly TB, were a common feature in the recruited patients, with the study group bearing a higher TB burden than the control group.

Majority of the patients with AIDS-KS presented with the disseminated form of the disease. Most of them also had mixed lesions. AIDS-KS usually follow an aggressive and fulminant course with involvement of multiple sites.^{13,21} Eventually, most patients with epidemic KS develop disseminated disease. Progression often proceeds in an orderly fashion from a few localized or widespread muco-cutaneous lesions to more numerous lesions and generalized skin disease with lymph node, gastrointestinal tract disease and other organ involvement. Pleuropulmonary KS is an ominous sign usually occurring late in the course of the disease, especially in those patients whose death is directly attributed to KS. Most patients with AIDS-KS die of one or more complicating opportunistic infections.

One year mortality at our facility was 22.9% among the AIDS-KS patients. This high rate may be due not only to the fact that most of our patients presented with advanced HIV disease but also to the unavailability of cytotoxic therapy. Various clinical and laboratory features of HIV-associated KS are associated with survival and have been used to develop KS staging systems. In multivariate analysis, only the CD4 count and tumour extent were significantly associated with survival; however, an additional analysis indicated that a lower CD4 count (i.e. 150 cells/mm³) was a better prognostic discriminant for survival than the originally proposed 200 cells/mm³ cut-off.^{22,23} Other indices such as BMI and duration of HAART use did not differ significantly between the two groups in our study.

Sub-Saharan Africa currently bears the brunt of the HIV pandemic. As HAART becomes more accessible following the implementation of the universal access initiatives, subsidizing treatment for significant opportunistic diseases and malignancies would become additional challenges as more patients with multiple pathologies will begin to access treatment and care in resource-limited settings like ours. Although no universally effective therapy for KS is available, treatment must be tailored to the individual patient, taking into consideration the extent of the disease and other co-morbidities. Response to specific treatment for AIDS-KS is higher when given in combination with HAART.

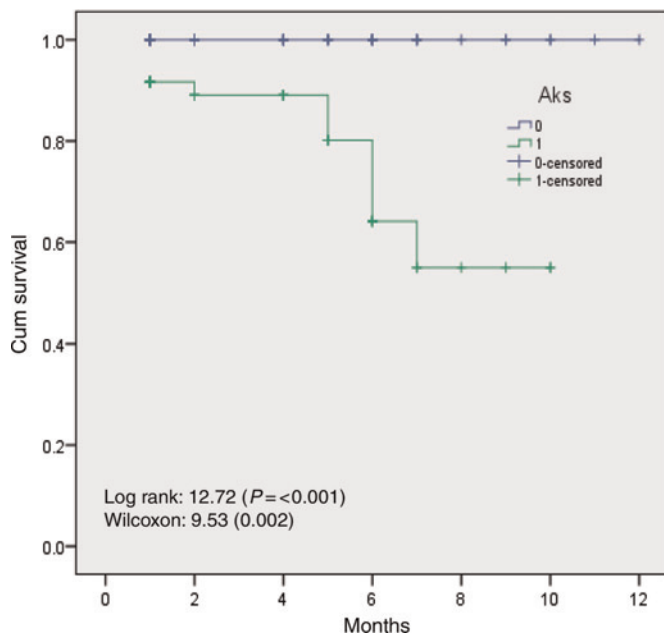


Figure 1 Cumulative survival of HIV-infected patients with and without AIDS-related Kaposi's sarcoma (AIDS-KS) in Jos, Nigeria

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(Accepted 27 October 2008)