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UPDATE

Kaposi Sarcoma in HIV Infected Patients

Jipa Raluca, Săndulescu Oana, Manea Eliza, Benea Şerban, Benea Otilia, Hristea Adriana*

National Institute of Infectious Diseases "Prof. Dr. Matei Balş", Bucharest, Romania; "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Objective: The aim of the study was to describe clinical and laboratory characteristics in HIV-infected patients with Kaposi sarcoma (KS). **Methods**: We retrospectively studied data on HIV-infected patients hospitalized in one tertiary care hospital in Bucharest, Romania, in whom Kaposi Sarcoma was diagnosed, between January 2008 and November 2013. **Results**: We identified 27 HIV-infected patients diagnosed with KS within 6 years. They had a median age of 42 years old and a median CD4 cell count of 101 cells per mm^3 at the time of KS diagnosis. All patients received antiretroviral therapy (ART), with 18 patients (66%) already on ART at the time of KS diagnosis. Most patients (59%) were classified as ACTG poor-risk and 56% as Mitsuyasu stage I. The overall prognosis was poor, with 41% mortality, in a median time span of 6 months, significantly correlated with gastrointestinal involvement (p=0.019), poor-risk KS in ACTG classification (p<0.001) and stage IV Mitsuyasu (p=0.006). **Conclusion**: KS remains an important cause of morbidity and mortality in patients with HIV infection, especially in late presenters.

Keywords: Kaposi disease, HIV, late presenters

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Introduction

Kaposi sarcoma (KS) is a vascular tumor etiologically associated with human herpes virus 8 (HHV-8) [1]. KS was one of the first recognized Human Immunodeficiency Virus (HIV)-related illnesses in the early 1980s and is the second most frequent tumor associated with Acquired Immunodeficiency Syndrome (AIDS) [2]. KS's clinical course can range from minimal mucocutaneous lesions with or without associated extremity lymphedema to a rapidly progressing disease with frequent extracutaneous involvement of the mucous membranes, gastrointestinal tract and respiratory tract [3] that can lead to significant morbidity and mortality. Since the introduction of highly active antiretroviral therapy (HAART) the incidence of KS decreased dramatically, from 14.3% during 1980 - 1989 to 1.8% during 1996 - 2006 [4]. According to the European Center for Diseases Control (ECDC), between 2008-2013, 2132 cases of KS were reported among HIV-infected patients [5].

The aim of our study was to describe clinical and laboratory characteristics and to assess predictors for death in KS HIV-infected patients.

Methods

We performed a retrospective, observational study of HIV-infected patients hospitalized in one tertiary care hospital in Bucharest, Romania, in whom KS was diagnosed, between January 2008 and November 2013. The diagnosis of KS was based on physical examination and skin biopsy. To determine visceral involvement we used an individualized approach consisting of upper endoscopy, bronchoscopy and/or computed tomography.

KS was staged according to the AIDS Clinical Trials Group (ACTG)[6] and the Mitsuyasu classification system [7]. According to the ACTG, KS was divided into good-risk (noted by subscript 1) or poor-risk (noted by subscript 0) depending on the extent of the tumor (T0- KS confined to skin and/or lymph nodes and/or minimal oral disease; T1 – widespread lesions of KS) the status of the immune system (I0 – CD4 cell count ≥200 cells/mm^3; I1 – CD4 cell count <200 cells/mm^3) and the extent of involvement within the body or systemic illness (S0/S1).

In accordance to Mitsuyasu staging we stratified patients into: stage I-localized nodular KS, with >15 cutaneous lesions or involvement restricted to one bilateral anatomic site and few, if any, gut nodules; stage II-includes both exophytic destructive lesions and locally infiltrative cutaneous lesions as locally aggressive KS; stage III-generalized lymphadenopathic KS with widespread lymph node involvement, with or without skin lesions, but with no visceral involvement; stage IV-disseminated visceral KS, usually progressing from stage II or stage III, with involvement of multiple visceral organs, and further into two subtypes: type A indicated the absence and type B the presence of "B" constitutional symptoms or opportunistic infections.

We used for prognostic a score proposed by Stebbing [8] in 2006: KS as the AIDS-defining illness (-3 points) and increasing CD4 count (-1 point for every complete 100 cells/mm^3) improved diagnosis, age of 50 year or older (2 points) and having another AIDS-defining illness at the same time (3 points) were associated with poor prognosis.

The whole group was followed-up for two years. Patients lost to follow-up were not included in the survival analysis.

Statistical analysis was performed with SPSS v. 19.0 (Statistical Package for the Social Sciences Inc, IBM Corp, Armonk, NY, USA). The Mann-Whitney *U*-test was used to analyse the differences between groups for continuous

* Correspondence to: Adriana Hristea
E-mail: adriana_hristea@yahoo.com

variables. For categorical variables, the χ^2 test or Fisher's exact test were used to test for differences between groups. The level of statistical significance was set at α=0.05. Survival distribution was estimated using the Kaplan-Meier method.

Results

We identified 27 HIV-infected patients diagnosed with KS between January 2008 and November 2013. There was a male predominance in our study group, with an overall male to female sex ratio of 2:1. At the time of KS diagnosis the median CD4 count was 101 cells/mm^3 (IQR 41-270) and the HIV viral load was 151,704 copies/mL (IQR 92,317-398,500). Patient's characteristics are shown in table I.

HIV infection was diagnosed before KS in 19 patients (70%), with a median time between HIV diagnosis and KS diagnosis of 19 months (IQR 0-58). In the remaining eight patients (30%) KS was the first AIDS-defining illness.

Ten patients who were on ART, with a median duration of time between ART and KS diagnosis of 32 months had virological failure, due to non-adherence. The median CD4 count decreased from 200 cells/mm^3 at the time of HIV diagnosis to 52 cells/mm^3 at the time of KS diagnosis in this group. In the remaining nine patients who were on ART, the median CD4 count increased from a median of 200 cells/mm^3 at the time of HIV diagnosis to 330 cells/mm^3 at the time of KS diagnosis, with a median duration of treatment of nine months. Eight out of nine (8/9) patients who were adherent to treatment and were on regimens with nucleoside reverse-transcriptase inhibitors (NRTIs) and protease inhibitors (PIs). Patients in whom KS was the first AIDS-defining illness had a median CD4 count of 62 cells/mm^3.

Regarding KS staging, 41% had T0 disease, 33% had I0 disease and 15% had S0 disesease. Twenty-one patients (78%) were in Mitsuyasu stage I and II.

Eleven patients (41%) patients received topical steroid therapy, with a median duration of three months. Six (22%) patients received specific treatment for KS: three local radiotherapy and three systemic therapy (two with interferon and one with liposomal doxorubicin).

The overall mortality was 41% (11/27), with a median duration between KS diagnosis and death of 6 months (IQR 2-15). Among patients who received specific treatment for KS, one (17%) patient died, 15 months after the diagnosis of KS. The Kaplan-Meier estimates of the probability of survival were 77% (95% CI 57-90) at 6 months, 69% (95% CI 48-84) at 12 months and 64% (95% CI 44-81) at 24 months. Figure 1 shows the overall cumulative probability of survival of HIV infected patients with KS.

Gastrointestinal involvement (p=0.019), CD4 count <200 cells per mm^3 (p=0.042), poor-risk KS in ACTG classification (p<0.001) and stage IV Mitsuyasu (p=0.006) have been shown in univariate analysis to be associated with mortality (table II).

Table I. Patient's characteristics, clinical manifestations and staging

Patient characteristics	N (%)	Clinical manifestations	N (%)	Staging	N (%)
Cutaneous KS localization		*Concomitant opportunistic infections*		*ACTG staging*	
Thorax	2 (7)	CMV retinitis	4 (15)	Good-risk KS	11 (41)
Facial	2 (7)	Oropharyngeal candidiasis	7 (26)	Poor-risk KS	16 (59)
Lower limbs	16 (59)	Pulmonary tuberculosis	7 (26)	*Mitsuyasu classification system*	
Disseminated	7 (26)	Pneumocystosis	4 (15)	Stage I	15 (56)
Oral mucosal lesions	10 (37)	Cerebral toxoplasmosis	1 (4)	Stage II	6 (22)
Gastrointestinal involvement	4 (15)	*Other malignancies*		Stage III	1 (4)
Pulmonary involvement	3 (11)	Cerebral lymphoma	1 (4)	Stage IV	5 (18)
Male	18 (67)	Gastric lymphoma	1 (4)	Subtype A	23 (85)
Age(years) (median, IQR)	42 (34-52)	Pancreatic carcinoma	1 (4)	Subtype B	4 (15)

ACTG = AIDS Clinical Trials Group; CMV = cytomegalovirus; KS = Kaposi sarcoma

Table II. Clinical and laboratory characteristics associated with death

	Favorable outcome N=16	Mortality related and unrelated to KS N=11	p value
Male, N (%)	8 (50)	10 (91)	0.042
Age (years) (median, IQR)	43 (35-52)	37 (21-61)	0.604
KS-AIDS defining illness, N (%)	4 (25)	4 (36)	0.675
Disseminated cutaneous lesions, N (%)	4 (25)	4 (36)	0.675
T1 stage, N (%)	9 (56)	7 (64)	1.000
S1 stage, N (%)	12 (75)	11 (100)	0.123
I1 stage, N (%)	8 (50)	10 (91)	0.042
GI involvement, N (%)	0 (0)	4 (36)	0.019
Pulmonary involvement, N(%)	0 (0)	3 (27)	0.056
Concomitant opportunistic infections, N (%)	6 (38)	7 (64)	0.103
ACTG poor-risk KS, N (%)	5 (31)	11 (100%)	<0.001
Stage IV Mitsuyasu, N (%)	0 (0)	5 (45)	0.006
On ART, N (%)	16 (100)	8 (73)	0.056

ACTG = AIDS Clinical Trials Group; ART = antiretroviral therapy; GI = gastrointestinal; KS = Kaposi sarcoma

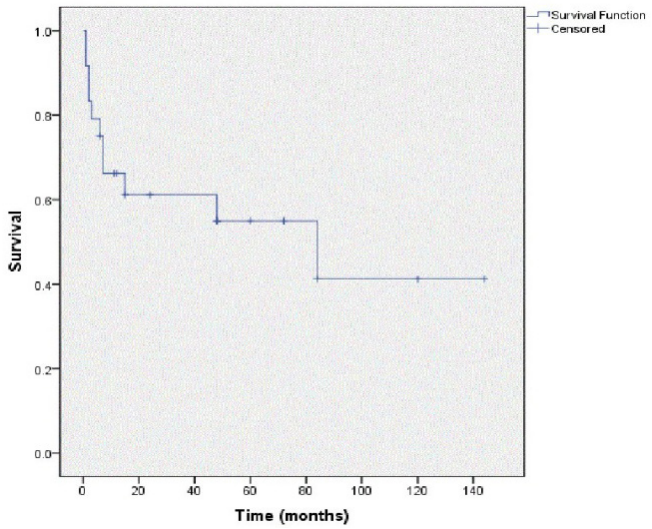

Fig. 1. Probability of survival

Using the prognostic index for AIDS-associated KS mortality proposed by Stebbing [8] , we found that 30% (8/27) of our patients were high risk as judged by his score (score >12 points) and only 7% (2/27) were patients with low risk (score <5 points). In individuals with low-risk prognostic scores, medium-risk and high risk, respectively, the probability of survival at 1-year was 1.0, 0.76 and 0.5, respectively.

Discussions

In our study KS was diagnosed in young patients with a median age of 42 years, with advanced HIV disease (AHD), with a median CD4 cell count of 101 cells/mm^3. Between January 2012 and December 2013, in Bucharest, Romania, 37% of the patients notified with HIV infection had AHD [9].

KS has been associated with HHV-8 infection, with the virus being always present in the tumor [10]. HHV-8 infection and KS are more common among HIV-positive men who have sex with men (MSM) or bisexual men, women who were infected with HIV through sex with bisexual men.

In a case-control study performed in Portugal, the mean age at diagnosis of AIDS-defining cancers (ADCs) was 41 years, and the mean CD4 cell count was 278 cells/mm^3; KS was the most frequent (61%) of ADCs [11].

A recent study has reported a high incidence of Kaposi sarcoma during the first 3 months of ART, describing KS as one of the manifestations of immune reconstitution inflammatory syndrome (IRIS) [[12]. In our study, the median time from ART initiation to KS diagnosis was 5 months (IQR 0-39); roughly half of our patients who were on ART (10/19) were in virological failure at the time of KS diagnosis and in the other 9/19 patients KS could have been an IRIS manifestation.

Patients in this study presented with extended mucocutaneous lesions and disseminated visceral involvement and 59% had poor-risk KS, a similar proportion to that reported in limited resource countries [13,14].

The overall mortality in the study group was 41%, associated with a short time span from KS diagnosis to death, of six months, similar to the pre-ART era. This is in part due to the fact that over half of the patients were staged as poor-risk (ACTG). All patients who died were classified as having poor-risk KS. Out of the other five patients classified as poor-risk KS, four had a favorable outcome and one was lost to follow-up. All patients who died had one or more opportunistic infections; tuberculosis, *Cytomegalovirus* and *Pneumocystis carinii* infection were the most frequent.

Our patients had poor access to specific therapy for KS. Only two patients received interferon and one received liposomal doxorubicin. Three patients received local radiotherapy. Poor access to specific therapy places us at the same level as Sub-Saharan Africa.

Overall cumulative survival was 69% at 1 year and 64% at 2 years, similar data being reported from a primary care HIV programme in South Africa [15]; however, the survival in our study proved to be lower compared to data reported from Chelsea and Westminster Hospital in London, UK [16].

Using Stebbing's prognostic index for AIDS-associated KS [8] regarding the probability of survival, we found similar values compared to Stebbing's study.

HAART can also lead to complete resolution of KS lesions in patients with good immunological response and limited disease [17]. Simultaneous systemic chemotherapy is indicated in patients with advanced, symptomatic KS [18]. The positive effect of ART on survival in patients with AIDS-associated KS is well known [19]. A large study of 326 individuals with AIDS-KS also found that mortality was not influenced by the initiation of ART before development of KS [6], similar to the data derived from our study group. In Stebbing's study [8], 80% of the patients had KS as the first AIDS-defining illness. KS as the first AIDS-defining illness and a higher CD4 counts were significantly associated with a better survival. In our study, in which 30% of the patients had KS as the first defining illness, mortality was significantly associated with CD4 count under 200 cells/mm^3 .

The retrospective nature and the small number of patients are intrinsic limitations; since gastrointestinal and/or pulmonary involvements are usually asymptomatic in HIV-related KS [20,21], the rate of organ involvement may have been clinically underdiagnosed. However, our results describe an aspect of the clinical picture for late-presenter HIV-positive patients diagnosed with KS, with severe evolution and rapid progression of disease.

Conclusion

In our HIV population, KS remains an important cause of morbidity and mortality especially in late presenters. The high mortality rate in this study population was as-

sociated with poor immunological status, extended KS and high incidence of opportunistic infections. Poor access to specific systemic treatment may have contributed to the high mortality rate and remains an important challenge in our clinic. For patients with disseminated, progressive or symptomatic disease, chemotherapy along HAART is an important component of the treatment.

Conflict of interest

None to declare

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