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A comparative study of classic and HIV-viremic and aviremic AIDS Kaposi sarcoma

David Séverin^a, Faiza Bessaoud^{c,*}, Nadia Meftah^d, Aurelie Du Thanh^a, Brigitte Tretarre^c, Bernard Guillot^a and Alain Makinson^b

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Background: Kaposi sarcoma in people living with HIV (PLHIV) is the most common AIDS-associated malignancy. There is increased interest in Kaposi sarcoma in PLHIV with controlled HIV viremia.

Objectives: To describe Kaposi sarcoma occurring in PLHIV despite virological control and to compare their clinical presentations with viremic AIDS-Kaposi sarcoma (AIDS-KS) and classic Kaposi sarcoma (CKS).

Methods: This was a monocentric retrospective study, including all Kaposi sarcoma patients registered between the 1 January of 2000 and 31 December 2017 in a comprehensive data bank for all cancers in the Hérault region, South of France. AIDS-KS were also described using chart reviews from the Infectious diseases Department, which followed more than 90% of PLHIV from the same region. We defined aviremic AIDS-KS as Kaposi sarcoma occurring in persons taking HAART with a HIV viral load less than 50 copies for more than 12 months. We compared clinical characteristics of persons with aviremic AIDS-KS, viremic AIDS-KS and CKS, using the Kriegel score and number and topography of skin lesions, and presence of lymphedema.

Results: We retrieved 187 Kaposi sarcoma cases, of which 12 occurred in PLHIV with aviremic AIDS-KS. Kriegel score stage I was found in 10 (83%) of the aviremic AIDS-KS, 34 (68%) of CKS and 38 (58.4%) of viremic AIDS-KS cases, with similar clinical presentations between aviremic AIDS-KS and CKS groups, and viremic AIDS-KS persons having more aggressive presentations. One person with aviremic AIDS-KS had visceral involvement.

Conclusion: We showed that Kaposi sarcoma in PLHIV with controlled viremia were generally indolent, similarly to CKS. Visceral involvement is, however, possible.

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Keywords: AIDS, classic Kaposi, controlled HIV viremia, HAART, HIV, Kaposi sarcoma

Introduction

Kaposi sarcoma is an angioproliferative tumor of endothelial origin, induced by the virus Kaposi

sarcoma-associated Herpesvirus or Human Herpes Virus-8 [1]. Four major clinical forms are described: classic (or Mediterranean) Kaposi sarcoma (CKS), mostly affecting elderly men of Mediterranean, east European, or

^aDepartment of Dermatology, Inserm U1058, ^bDepartment of Infectiology, Inserm U1175, Saint Eloi Hospital and Montpellier University Hospital, ^cHérault Tumor Registry, and ^dCOREVIH, Saint Eloi Hospital and Montpellier University Hospital, Montpellier, France.

Correspondence to Dr David Séverin, Department of Dermatology, Saint Eloi Hospital and Montpellier University Hospital, 80 avenue Augustin Fliche, 34090 Montpellier, France.

E-mail: severin.david.michel@gmail.com

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Jewish heritage with a peak incidence after the sixth decade of life; endemic African Kaposi sarcoma, occurring in sub-Saharan Africa among children and adults; iatrogenic immunosuppressive Kaposi sarcoma affecting patients receiving chronic immunosuppressive therapy, mostly organ-transplant recipients; and Epidemic Kaposi sarcoma or AIDS-KS, the most common AIDS-associated malignancy in people living with HIV (PLHIV) [1,2].

In France and in southern Europe, before the AIDS epidemic, the most frequent form of Kaposi sarcoma was CKS, occurring sporadically. After the AIDS epidemic, Kaposi sarcoma incidence increased in all Western countries and AIDS-KS became the first incident Kaposi sarcoma in Europe [3–6].

With the advent of HAART, AIDS-KS incidence decreased [7–9], through the effects of improved immunity and controlled viremia [10,11]. Some Kaposi sarcoma can develop in PLHIV taking HAART [12–14] but most of these cases are generally attributed to persistent low CD4⁺ cell counts during the first year of HAART initiation or HAART failure [15]. There have also been recent reports of Kaposi sarcoma cases in PLHIV with high CD4⁺ cell count and controlled HIV-1 RNA viral load under HAART [13,16,17]. Though the pathophysiology is unclear, immunosenescence and permanent loss of the anti-HHV8 immune response despite partial T CD4⁺ restoration under HAART are possible mechanisms [18]. As the PLHIV are aging, incidence of Kaposi sarcoma with controlled viremia could increase with time. Additional descriptions of clinical spectrums of Kaposi sarcoma in PLHIV with controlled viremia are needed.

We aimed to describe all Kaposi sarcoma occurring in PLHIV despite virological control under HAART and compared these cases with HIV-viremic AIDS-KS and CKS in the Hérault Department in France, a region of 1.14 million inhabitants in 2017.

Materials and methods

Study populations

This is a retrospective study including all Kaposi sarcoma patients diagnosed between the 1 January of 2000 and 31 December 2017. Non-AIDS cases were identified through the Hérault's Cancer Registry, a register, which constitutes all histologically diagnosed cancers in the French Hérault region, and which participates in the national cancer registry network (FRANCIM). As histological diagnosis is not mandatory for Kaposi sarcoma diagnosis in PLHIV, HIV cases were included through a clinical registry used for PLHIV in the Department of Infectious Diseases. This department

follows around 90% of the PLHIV in the Hérault area, thus including most Kaposi sarcoma in PLHIV in the same period and in the same geographic area as CKS cases.

Inclusion criteria and definition

We excluded cases of Iatrogenic and African endemic Kaposi sarcoma, because of their small numbers and alternative pathophysiology, and undefinable cases. Participants were categorized according to their Kaposi sarcoma clinical form: CKS and AIDS-KS. Among PLHIV with AIDS-KS, those being on HAART with an HIV RNA viral load less than 50 copies/ml for more than 12 months were categorized as 'aviremic-AIDS-KS'. Those having an AIDS-KS and virological replication, whether taking antiretroviral therapy or not, or those with a viral load less than 50 copies/ml for less than 12 months were categorized as viremic AIDS-KS. As Kaposi sarcoma can have recurrences, only the first CKS or AIDS-KS were described. However, a person with aviremic AIDS-KS could have had a history of viremic AIDS-KS prior to efficacious HAART.

We compared CKS, aviremic AIDS-KS and viremic AIDS-KS using the Kriegel score as the main outcome for severity [19]: stage I – locally indolent Kaposi sarcoma cutaneous lesions; stage II – locally invasive and aggressive form; stage III – disseminated mucocutaneous form, often with lymph node involvement; and stage IV – disseminated, mucocutaneous form with visceral involvement.

We used the following secondary outcomes as additional severity scores:

- (1) total number of objectified skin lesions at Kaposi sarcoma diagnosis (<5, 5–20, >20 lesions on body)
- (2) topography of lesions (head and neck, trunk, upper limbs, lower limbs, oral mucosa and genital mucosa)
- (3) presence of lymphedema

The following variables were collected at Kaposi sarcoma diagnosis: demographic data (age, sex), year of HIV diagnosis, HIV RNA viral load, lymphocyte T CD4⁺ cell count and lymphocyte T CD8⁺ cells count, HBV and HCV infection defined by the presence of HBs Ag and anti-HCV antibodies, high blood pressure (HBP), diabetes and treatments. Three calendar periods were defined for year of HIV diagnosis: prior to 1996, between 1996 and 2000 and after 2000. These periods correspond to the advent of first generation HAART in 1996 in France and starting in 2000, the spread of second generation boosted protease inhibitors.

Statistical analysis

The comparison of the groups with respect to the qualitative variables was based on the chi-square test or

Fisher's exact test. The comparison of the groups with the quantitative variables was based on analysis of variance (ANOVA) when the conditions of normality (Shapiro–Wilk test) and homoscedasticity (Bartlett's test) were verified. Under this condition, the comparative analysis used the Kruskal–Wallis test. All *P* values presented are two-sided, and those less than 0.05 were considered statistically significant. All statistical analyses were performed with the R software (R Foundation, Vienna, Austria).

Results

In total, we counted 187 Kaposi sarcoma cases between 2000 and 2017. There were 109 PLHIV with a diagnostic of AIDS-KS (58.3%), and 62 CKS (33.2%). After exclusion, a total of 142 persons were kept for analysis: 62 CKS and 80 AIDS KS patients amongst whom 12 were aviremic AIDS-KS (see flow chart on Fig. 1). Main characteristics are summarized in Table 1.

Main characteristics of aviremic AIDS-Kaposi sarcoma

Kaposi sarcoma was a first episode of AIDS-KS in 5 of the 12 aviremic AIDS-KS patients (41.7%) and a recurrent episode in 7 patients, with prior viremic AIDS-KS (58.3%). These patients were all men. The median age at Kaposi sarcoma diagnosis was 54 years [interquartile range (IQR) 38–60]. The median time laps between HIV diagnosis and aviremic AIDS-KS diagnosis was 8.2 years. Only one person had a CD4⁺ cell count less than 400/ μ l,

setting the median at 723/ μ l (IQR, 520–881). Median CD8⁺ cell counts were 727/ μ l (IQR 671–1317), and median CD4⁺/CD8⁺ ratio 0.68 (IQR, 0.52–0.94).

Ten of the 12 (83%) aviremic AIDS-KS had Kriegl score stage I (locally indolent cutaneous lesions), and eight persons (66.6%) presented themselves with less than five cutaneous lesions. All participants had less than 20 cutaneous lesions. Cutaneous lesions mainly occurred in lower limbs in nine (75%) of cases, and one showed lymph node (stage III) and one visceral lesions (pulmonary, stage IV)). No cases of lymphedema were noted.

Two cases needed chemotherapy: one with the lymph node involvement, and one with the visceral involvement. Five persons were treated with local therapy, and for the other five no treatments were introduced.

Characteristics of classic (or Mediterranean) Kaposi sarcoma group

Sixty-two CKS cases were diagnosed (48 in male and 14 in female individuals). The median age at the time of diagnosis was 71 years (IQR, 64–80).

Most of the patients presented with a nonaggressive disease: Kriegl score stage I in 68% of cases, and with less than 20 lesions in 92%. Only two patients (4%) presented lymph node involvement (stage III) and four patients (8%) had visceral involvement, gastric and pulmonary lesions (stage IV). Ten patients (19.2%) did not undergo any treatment, but most [35 patients (67%)] underwent local therapy [cryotherapy 14 (27%), surgery 14 (27%), radiotherapy 6 (11.5%), laser 1 (1.9%)]. Fourteen patients

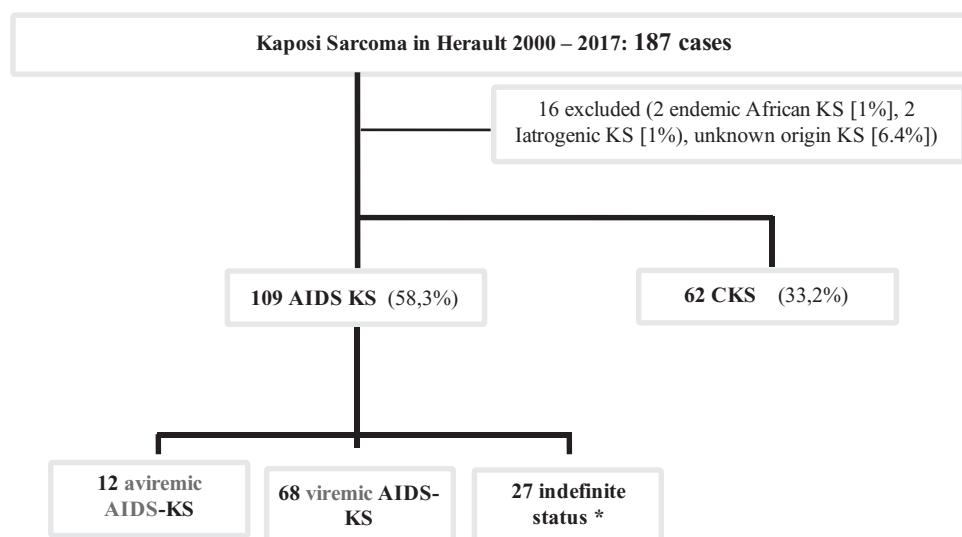


Fig. 1. Flow chart. AIDS-KS, AIDS-associated Kaposi sarcoma; aviremic AIDS-KS, people living with HIV being on HAART continuously and with an HIV RNA viral load less than 50 copies for more than 12 months aviremic; CKS, classic Kaposi sarcoma; KS, Kaposi sarcoma. *Data was not precise enough to determine if cases were aviremic AIDS-KS or viremic AIDS-KS. Unknown origin Kaposi sarcoma, cases of Kaposi sarcoma identified through the Herault Cancer Registry but for whom we were not able to determine the type of Kaposi sarcoma.

Table 1. Patient characteristics.

Variables	Viremic AIDS-KS (n = 68)	Aviremic AIDS-KS (n = 12)	CKS (n = 62)	P (aviremic AIDS-KS vs. viremic AIDS-KS)	P*(aviremic AIDS-KS vs. CKS)
Age at KS diagnostic (median [range])	39 [33–46]	54 [38–60]	71 [64–80]	0.019	<0.0001
Sex				0.58	0.11
Male	62 (91.2%)	12 (100%)	48 (77.4%)		
Female	6 (8.8%)	0	14 (22.6%)		
HBP	4 (5.9%)	4 (33.3%)	16 (37.2%)	0.016	
Diabetes	1 (1.49%)	1 (8.3%)	9 (20.4%)	0.28	0.67
HVB	3 (4.4%)	0	0		
HVC	5 (7.35%)	1 (8.3%)	1 (1.61%)		
Kriegel score				0.42	0.27
I	38 (58.4%)	10 (83.3%)	34 (68%)		
II	7 (10.8%)	0	10 (20%)		
III	6 (9.2%)	1 (8.3%)	2 (4%)		
IV	14 (21.5%)	1 (8.3%)	4 (8%)		
Missing data	0	0	12		
Number of cutaneous lesions				0.040	0.68
<5	22 (33.8%)	8 (66.6%)	27 (54%)		
5–20	25 (38.4%)	4 (33.3%)	19 (38%)		
>20	18 (23.4%)	0	4 (8%)		
Missing data	3	0	12		
Topography of the lesions					
Lower limbs	34 (52.3%)	9 (75%)	42 (84%)	0.2	0.43
Unilateral	6 (9.2%)	5 (41.7%)	17 (34%)	0.011	0.73
Bilateral	28 (43.1%)	4 (33.3%)	25 (50%)	0.75	0.35
Upper limbs	42 (65.6%)	6 (50%)	17 (34%)	0.34	0.33
Unilateral	17 (26.6%)	3 (25%)	10 (20%)		0.70
Bilateral	25 (39%)	3 (25%)	7 (14%)	0.51	0.39
Trunk	33 (50.8)	1 (8.3%)	5 (10%)	0.009	
Head and neck	18 (28.1%)	3 (25%)	4 (8%)		0.12
Mucosa	23 (35.4%)	0	3 (6%)	0.014	
Oral mucosa	21 (32.3%)	0	2 (4%)	0.03	0.48
Genital mucosa	2 (3%)	0	1 (2%)		
Lymph node involvement	12 (18.5%)	1 (8.3%)	2 (4%)	0.67	
Visceral involvement	14 (21.5%)	1 (8.3%)	4 (8%)	0.44	
Missing data	0	0	12		
Lymphedema	3 (4.6%)	0	9 (18%)		0.18
Missing data	0	0	12		
Treatments					
Abstention ^a	1 (1.56%)	5 (41.7%)	10 (19.2%)	0.0002	0.13
Local therapy ^b	4 (6.2%)	5 (41.7%)	35 (67.3%)	0.015	0.29
Chemotherapy	28 (43.8%)	2 (16.7%)	14 (26.9%)	0.078	0.71
HAART ^c	31 (48.4%)	0	0	0.001	
Missing data	0	0	10		

Aviremic KS, Kaposi sarcoma; CKS, classic Kaposi sarcoma; HBP, high blood pressure; HVB, hepatitis virus B; HVC, hepatitis virus C.

^aNo specific treatment was used for Kaposi sarcoma, which means no additional treatment if patients were on HAART.

^bCryotherapy, radiotherapy, surgery, local retinoids and laser.

^cHAART introduced and used as unique KS treatment.

*P value evaluation excludes missing data.

(27%) needed chemotherapy (with either bleomycin, doxorubicin, docetaxel or daunoxome).

Characteristics of viremic AIDS-Kaposi sarcoma group

We counted 109 incident diagnosis of viremic AIDS-KS. For 27 patients, biological and clinical data were missing and persons were thus excluded from analysis. In total, PLHIV with viremic AIDS-KS were 68 (62 male and 6 female individuals). The median age was 39 years (IQR, 33–46).

Twenty patients (30.7%) presented an aggressive disease, stage III Kriegel score in 9.2% and stage IV in 21.5%. Upper limbs were the main topography of skin lesions

(66%), followed by lower limbs (53%) and trunk (51%). There were 23 patients with mucosa lesions (35%) and 18 with head and neck skin lesions (28%). Nearly half of viremic AIDS-KS patients had their Kaposi sarcoma treated only with HAART (48%), the rest being treated with chemotherapy (42%). Biological data are summarized in Table 2.

Comparison of the aviremic AIDS-Kaposi sarcoma with the other groups

There were no significant differences between aviremic AIDS-KS and CKS groups in terms of clinical presentation, except for the age at diagnosis ($P < 0.0001$) (Table 1). Both groups predominantly had a localized indolent disease, but 17% of aviremic AIDS-KS and

Table 2. Comparison of HIV-related characteristics between viremic and aviremic AIDS-KS.

Variables	Aviremic AIDS-KS (n = 12)	Viremic AIDS-KS (n = 68)	P
Age at HIV diagnosis (median [range])	37 [29–47]	32 [26–42]	0.29
Time (years) between HIV dg and Kaposi dg (median [range])	8.2 [4.6–20.6]	2.5 [0.4–9.4]	0.008
PLHIV under antiretroviral therapy (%)	12 (100)	13 (19.1)	<0.0001
HIV RNA viral load (copy/ml)			<0.0001
<50	12 (100%)	0	
>400	0	68 (100%)	
CD4 ⁺ lymphocyte cell count (median [range])	723 [520–881]	122 [25–233]	<0.0001
CD8 ⁺ lymphocyte cell count (median [range])	727 [671–1317]	777 [426–987]	0.24
CD4 ⁺ /CD8 ⁺ ratio (median [range])	0.68 [0.52–0.94]	0.14 [0.05–0.30]	<0.0001
Time of HIV diagnostic			0.59
<1996	5 (41.7%)	20 (29.8%)	
1996–2000	1 (8.3%)	15 (22.4%)	
>2000	6 (50%)	32 (47.8%)	

Aviremic AIDS-KS, people living with HIV with a diagnostic of Kaposi sarcoma while being on HAART continuously and with an HIV RNA viral load less than 50 copies for more than 12 months; Viremic AIDS-KS, people diagnosed with AIDS-related Kaposi sarcoma and who did not have virological control or viral load less than 50 copies for less than 12 months.

12% of CKS had disseminated disease (stage III and IV Kriegel). The distribution of skin lesions was similar in both groups, in lower limbs for 75% in aviremic AIDS-KS and 84% in CKS. Most persons presented less than five skin lesions (67% in aviremic AIDS-KS and 54% in CKS).

There was a tendency for viremic AIDS-KS PLHIV to have more aggressive presentation in comparison with aviremic AIDS-KS, as 14 PLHIV (22%) had a Kriegel score of 4 versus 1 PLHIV (8%) for aviremic AIDS-KS. Significant differences between persons with viremic AIDS-KS and aviremic AIDS-KS were objectified on the number of cutaneous lesions at diagnosis ($P=0.04$), and for unilateral lower limb (versus bilateral) involvement [five aviremic AIDS-KS (42%) versus six in viremic AIDS-KS (9%), $P=0.011$]. Also trunk topography of Kaposi sarcoma was significantly more frequent in viremic AIDS-KS [50 versus 8%, $P=0.009$], as were mucosal lesions [35% versus none, $P=0.014$]. The proportion of lymph nodes or visceral lesions was higher in viremic AIDS-KS group than in aviremic AIDS-KS group, though the difference was not significantly different (Table 1).

Viremic AIDS-KS PLHIV had received more chemotherapy than aviremic AIDS-KS patients (44 versus 17%), though the difference was not significant. Viremic AIDS-KS underwent less local treatment than aviremic AIDS-KS (6 versus 42%) ($P=0.015$).

Discussion

In this study of all Kaposi sarcoma cases, in the Hérault region between 2000 and 2017, we found that Kaposi sarcoma regularly occurred after HAART in PLHIV, even in persons with fully controlled RNA replication and high CD4⁺ cell counts. These persons clinically

resembled CKS cases, except for age. As expected, viremic AIDS-KS clinical presentation was more aggressive in comparison with aviremic AIDS-KS and CKS.

In 2003, one study tried to evaluate the clinical characteristics of Kaposi sarcoma occurring after HAART initiation [12]. They showed that patients already receiving HAART at the time of Kaposi sarcoma diagnosis had less aggressive presentation, especially in number of cutaneous lesions. More recently, Maurer *et al.* reported in 2007 nine HAART-treated cases with persistent cutaneous Kaposi sarcoma despite sustained CD4⁺ counts greater than 300 cells/ μ l and suppressed HIV viremia for at least 2 years [13]. Other studies described this specific type of HIV-related Kaposi sarcoma, focusing on epidemiological aspects, such as incidence rates and survival rates [14,20,21]. Recently an observational study by the French Cancer VIH group reported the clinical features of 21 cases of Kaposi sarcoma occurring in HAART-treated patients with suppressed HIV viremia. They showed that this type of Kaposi sarcoma had a less aggressive presentation than viremic AIDS-KS but could also be disseminated [17]. Contrary to our study, cases described by the multidisciplinary committee are not representative of AIDS-KS, as this committee deals only with complicated cases requiring expert national advice for management, thus selecting for more severe cases. Our study confirms that most cases of aviremic AIDS-KS are indolent, necessitating less aggressive treatments than viremic AIDS-KS.

A majority of both aviremic AIDS-KS and CKS groups underwent similar nonaggressive local therapy. Kaposi sarcoma cutaneous lesions do not necessarily need treatment. In CKS, lesions can stay quiescent for a very long time, and some rare cases of spontaneous regression have been reported [22,23]. Our study also confirmed the global indolent behavior of aviremic AIDS-KS under HAART. However, in both CKS and aviremic AIDS-KS,

cases of extensive Kaposi sarcoma were described with visceral involvement. Since its introduction, HAART has been used as a treatment of AIDS-associated Kaposi sarcoma, as immune restoration and virological control impede HHV-8 proliferation [10,11]. However, treatment of Kaposi sarcoma in aviremic AIDS-KS as in CKS with extensive lesions can be more challenging, as immunity will not improve [24].

The study also raises questions about physiopathology of Kaposi sarcoma in persons without evident or with low-grade immunodeficiency [25–27]. A study by Unemori *et al.* reported an association between immunosenescence and Kaposi sarcoma, even when controlling for confounders including age, CD4⁺ cell count, sex, HIV viral load and HHV8 status [28]. It has been previously suggested that Kaposi sarcoma is linked to deficiencies in specific anti-HHV-8 T-cell immunity through comparison of asymptomatic HHV8 carriers in PLHIV with PLHIV with Kaposi sarcoma [18]. This lack of anti-HHV-8-specific T-cell responses could contribute to the development of Kaposi sarcoma in PLHIV with suppressed viremia, exacerbated by immunosenescence. In CKS, affecting elderly men of Mediterranean, physiopathology is not fully elucidated but the hypothesis of an aging-related T-cell immune deficiency has been raised [29,30]. Our study probably reflects the strong reduction of viremic AIDS-KS but a possible increase in aviremic AIDS-KS with age and possible immune senescence.

In conclusion, in this analysis of all Kaposi sarcoma cases in the Hérault region between 2000 and 2017, our study showed that Kaposi sarcoma in HIV virologically controlled persons were not exceptional, were generally indolent, and resembled clinical presentations of CKS. Whether similar immunological mechanisms of senescence are responsible for both clinical presentations need to be further explored.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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