Mediterranean Journal of Hematology and Infectious Diseases

Letter to the Editor

Kaposi Sarcoma in People Living with HIV: Is it Water under the Bridge?

Keywords: Kaposi Sarcoma; HIV; AIDS; Mortality; Antiretroviral therapy.

Published: May 1, 2023 **Received: January 29, 2023** **Accepted: April 17, 2023**

Citation: Papalini C., Brescini L., Curci L., Bastianelli S., Barchiesi F., Giacometti A., Francisci D. Kaposi Sarcoma in people living with HIV: is it water under the bridge? Mediterr J Hematol Infect Dis 2023, 15(1): e2023027, DOI: http://dx.doi.org/10.4084/MJHID.2023.027

To the editor.

Kaposi Sarcoma (KS) in people living with HIV (PLWH) is an AIDS-defining malignancy implying endothelial cell proliferation. It can involve all the organs but most frequently appears as purplish or brownish mucocutaneous lesions. Herpesvirus-8 (HHV-8) is recognized as the primum movens of the oncogenic pathway. Men who have Sex with Men (MSM) and African inhabitants of the "KS belt" have the main risk factors for HHV-8 infection and KS.[1-5] Antiretroviral therapy (ART) has sensibly modified KS incidence. However, it is still one of the most frequent neoplasms in PLWH.[1,3,6,7]

The aim of this study is to report epidemiological and clinical features of PLWH affected by KS and to analyze which variables, if any, influence the mortality rate.

This retrospective observational study included PLWH affected by KS attending the Infectious Diseases Clinics of S. Maria della Misericordia Hospital of Perugia, Italy, or Torrette Hospital of Ancona, Italy, from Jan 1, 2002, to Dec 31, 2022. The two hospitals are the main health centers of two regions of Central Italy, Umbria, and Marche, and about 800 and 500 PLWH, respectively, visited their Infectious Diseases Clinics.

KS was diagnosed clinically and histologically, while data about HHV-8 viremia were unavailable for all the patients due to the study's retrospective nature.

Every patient provided consent for using his/her data at the hospital admission. For each one, we collected information about gender, age at HIV infection diagnosis, nationality, a risk factor for HIV acquisition, smoking attitude, HHV-8 positivity, HPV positivity, HCV antibodies positivity, HBV surface antigen (HBsAg) positivity, date of KS diagnosis and ART starting, CD4 cell count at the moment of HIV infection and KS diagnosis, viremia at the moment of HIV infection and KS diagnosis, CD4/CD8 ratio at KS diagnosis, ART regimen, chemotherapy administered, 5-year survival and eventually the date of death.

CD4 cell count and CD4/CD8 ratio were measured by cytofluorometry, while HIV RNA was tested by Real-time quantitative PCR, whose detectability threshold was 20 copies/ml. When HIV RNA was undetectable or under this threshold, to calculate the median value, we considered HIV viremia 0 or 19, respectively.

HBsAg and HCV antibodies were detected with chemiluminescent immunoassay, while HPV DNA on anal or cervical swabs and plasmatic HHV-8 DNA with semi-quantitative PCR.

Due to their asymmetrical distribution, continuous variables were presented as the median with IQR, while the categorical ones were expressed by their relative frequencies. A comparison was performed between patients who died and those who survived after 5 years from KS diagnosis. The Mann-Whitney U-test and the Chi-square test were used to compare differences between groups, as appropriate. A p-value <0.05 was considered relevant.

Results. In the considered period, the number of KS cases remained quite stable, and there was no increase in the post-SARS-CoV2 pandemic time lapse. Overall, 60 patients were affected by KS: 53 (88.3%) males and 7 (11.7%) females whose characteristics were summarised in **Table 1**. Fourty-5 (75%) were Italians, 9 (15%) were Africans, and 2 (3.3%) persons were from Eastern Europe, with a median age of 42 and 44 years at HIV and KS diagnosis, respectively. Some individuals also had other risk factors for malignancies: 19 (31.7%) smoked, 7 (11.7%), 7 (11.7%), and 18 (30%) were co-infected with HBV, HCV, and HPV, respectively. Regarding HIV transmission, 35 (58.3%) were MSM, 20 (33.3%) were heterosexual people, and 5 (8.3%) were intravenous drug users (IVDU) (**Table 1**).

At the moment of HIV infection diagnosis, 42 (70%) persons had HIV RNA over 100,000 copies/ml (median value: 224,000 copies/ml), 45 (75%), and 47 (78.3%) had CD4+ cell count below 200/µl (median value: 63/µl; IQR 19-135) and 350/µl, respectively. In 38 (63.3%) cases, Kaposi Sarcoma was the first sign of HIV infection, while in 21 (35%), it manifested later, and the

Table 1. Epidemiological and clinical characteristics of patients affected by KS.

	Males (n=53)	Females (n=7)	Total (n=60)
Nationality (%)			
Italian	42 (79.2)	3 (42.9)	**45 (75)**
African	5 (9.4)	4 (57.1)	**9 (15)**
East European	2 (3.8)	0	**2 (3.3)**
South American	2 (3.8)	0	**2 (3.3)**
West European	1 (1.9)	0	**1 (1.7)**
North American	1 (1.9)	0	**1 (1.7)**
Median age at HIV diagnosis (IQR)	44 (33.25-49.75)	29 (23-33)	**42 (32-49)**
Median age at KS diagnosis (IQR)	44 (34.75-50.75)	34 (32-46)	**44 (32-50)**
Risk factors (%)			
MSM	35 (66)	0	**35 (58.3)**
Heterosexual behaviour	15 (28.3)	5 (71.4)	**20 (33.3)**
IVDU	3 (5.7)	2 (28.6)	**5 (8.3)**
Smoking	16 (30.2)	3 (42.9)	**19 (31.7)**
HBV-coinfection	5 (9.4)	2 (28.6)	**7 (11.3)**
HCV-coinfection	5 (9.4)	3 (42.9)	**7 (11.3)**
HPV-coinfection	13 (24.5)	5 (71.4)	**18 (30)**
KS localization (%)			
Cutaneous	32 (60.4)	4 (57.1)	**36 (60)**
Mucosal	1 (1.9)	0	**1 (1.7)**
Cutaneous-mucosal	5 (9.4)	1 (14.2)	**6 (10)**
Disseminated	15 (28.3)	2 (28.7)	**17 (28.3)**
CD4 cell count at HIV diagnosis (%)			
<200	42 (79.2)	3 (42.9)	**45 (75)**
200-500	3 (5.7)	2 (28.6)	**5 (8.3)**
>500	2 (3.8)	1 (14.2)	**3 (5)**
Not available data	6 (35.3)	1 (14.2)	**7 (11.7)**
CD4 cell count at KS diagnosis (%)			
<200	34 (64.1)	3 (42.8)	**37 (61.7)**
200-500	7 (13.2)	2 (28.6)	**9 (15)**
>500	3 (5.7)	2 (28.6)	**5 (8.3)**
Not available data	5 (9.4)	0	**5 (8.3)**
CD4/CD8 ratio at KS diagnosis (%)			
<0.5	32 (60.4)	4 (57.1)	**36 (60)**
>0.5	3 (5.7)	2 (28.7)	**5 (8.3)**
Not available data	18 (34)	1 (14.2)	**19 (31.7)**
HIV RNA at HIV diagnosis (%)			
<100000	6 (11.3)	1 (14.2)	**7 (11.7)**
>100000	38 (71.7)	4 (57.1)	**42 (70)**
Not available data	9 (17)	2 (28.7)	**11 (18.3)**
HIV RNA at KS diagnosis (%)			
<100000	22 (41.5)	5 (71.4)	**27 (45)**
>100000	25 (47.2)	2 (28.6)	**27 (45)**
Not available data	6 (11.3)	0	**6 (10)**

*expressed as cells/µl; **expressed as copies/ml

diagnosis date of a patient was unknown (**Table 1**).

HHV-8 viremia was available for 20 individuals, and 15 resulted positive, while histology revealed KS in 6 patients. In 34 cases, both data were lacking.

KS localized on the skin in 36 (60%) patients, while 1 (1.7%), 6 (10%), and 17 (28.3%) had mucosal, cutaneous-mucosal, and disseminated forms, respectively. Furthermore, 12 patients were affected by additional cancerous or precancerous lesions: Castleman disease (2; 3.3%), primitive effusive Lymphoma (1; 1.7%), cervical (2; 3.3%), and anal intraepithelial neoplasms (1; 1.7%), non-Hodgkin Lymphoma (1; 1.7%), liver (1; 1.7%), prostate (1; 1.7%) and anal cancer (3; 5%).

At the moment of KS diagnosis, 37 (61.7%) patients had CD4 cell count <200/µl (median value: 96 cells/µl), 27 (45%) HIV viremia >100000 copies/ml (median value: 100000 copies/ml), 36 (60%) CD4/CD8 <0.5 while 17 (28.3%) were already on ART since a median of 212 days (**Table 1**).

This special group of people already on treatment included 13 (76.5%) males with a median CD4 nadir of 123 cells/µl (IQR 48.5-197). Their epidemiological and clinical data are shown in **Table 2**. The median interval from HIV diagnosis to ART starting was 1500 days (IQR 242.5-4306.5): 7 of them (41.7%) assumed PI-based ART; on the contrary, 4 (23.5%) the INI-based one.

Table 2. Epidemiological and clinical characteristics of patients already on ART at KS diagnosis.

Gender (%)	
Male	13 (76.5)
Female	4 (23.5)
Nationality (%)	
Italian	12 (70.6)
African	5 (29.4)
Median age (IQR)	
At HIV diagnosis	38 (28.5-46.5)
At KS diagnosis	46 (34-50.5)
Risk factors (%)	
MSM	7 (41.2)
Heterosexual behaviour	8 (47)
IVDU	2 (11.8)
Smoking	7 (41.2)
HBV-coinfection	2 (11.8)
HCV-coinfection	4 (23.5)
HPV-coinfection	5 (29.4)
KS localisation (%)	
Cutaneous	11 (64.7)
Mucosal	1 (5.9)
Cutaneous-mucosal	1 (5.9)
Disseminated	4 (23.5)
HHV-8	
Positive viremia	4 (23.5)
Positive histology	3 (17.6)
Not available data	9 (52.9)
Median CD4 cell count nadir* (IQR)	123 (48.5-197)
CD4 cell count* at HIV diagnosis (%)	
<200	9 (52.9)
200-500	3 (17.7)
>500	2 (11.7)
Not available data	3 (17.7)
CD4 cell count* at KS diagnosis (%)	
<200	6 (35.3)
200-500	6 (35.3)
>500	5 (29.4)
CD4/CD8 ratio at KS diagnosis (%)	
<0.5	9 (52.9)
>0.5	5 (29.4)
Not available data	3 (17.7)
HIV RNA at HIV diagnosis (%)**	
<100000	5 (29.4)
>100000	7 (41.2)
Not available	5 (29.4)
HIV RNA at KS diagnosis (%)**	
<50	8 (47.1)
>50	9 (52.9)
ART regimen (%)	
PI-based	7 (41.7)
INI-based	4 (23.5)
PI+INI-based	1 (5.9)

*expressed as cells/µl; ** expressed as copies/ml.

Thirty-4 patients (56.7%) were treated only with ART; on the other hand, 18 (30%) needed chemotherapy, 4 (6.6%) radiotherapy, and 3 (5%) surgery. The prevalent ART regimen was nucleoside reverse transcriptase (NRTI) and protease (PI) inhibitors (31 cases; 51.7%), followed by NRTI plus integrase inhibitors (INI) (9 cases; 15%), while 2 (3.3%) patients received NRTI with both PI and INI (**Table 1**). Overall, the median interval between HIV diagnosis and ART start was 17 days (IQR 0.25-57.5), and regimens based on NRTI and INI progressively increased during the considered period.

Five years after KS diagnosis, 46 (76.7%) individuals were still alive: 41 (89.1%) were male, 28 (60.9%) MSM; 5 (10.9%), 7 (15.2%) and 17 (37%) co-infected by HBV, HCV, and HPV, respectively; 14 (30.4%) smoked. Their median age was 40 at HIV diagnosis and 44 at KS diagnosis; 29 (63%) had cutaneous localization, and 26 (56.5%) were treated only with ART (**Table 3**).

Table 3. Mortality risk factors in KS patients.

	Dead at 5-year follow up (n=11)	Alive at 5-year follow up (n=46)	p
Male gender (%)	9 (81.8)	41 (89.1)	0.5115
Italian nationality (%)	7 (63.6)	35 (70.1)	0.4036
MSM sexual behaviour (%)	5 (45.4)	28 (60.9)	0.3564
Co-infections (%)			
HBV	1 (9)	5 (10.9)	0.9015
HCV	0 (0)	7 (15.2)	0.4225
HPV	1 (9)	17 (37)	0.1326
Smoking (%)	5 (45.4)	14 (30.4)	0.2325
Median age (IQR)			
at HIV diagnosis	46 (38-49)	40 (31.5-50)	0.27
at KS diagnosis	47 (39-61)	44 (32-50.25)	0.3232
Median CD4 count* (IQR)			
nadir	70 (61-168)	51 (18.5-138)	0.4788
at KS diagnosis	70 (37-340)	101.5 (27-241)	0.7911
Median HIV RNA (IQR)**			
at HIV diagnosis	519000 (184500-979750)	222000 (105000-578966)	0.1282
at KS diagnosis	144000 (65-843000)	85100 (91.5-466500)	0.5029
Median CD4/CD8 at KS diagnosis (IQR)	0.06 (0-6)	0.1 (0-4)	0.7006
Disseminated KS (%)	5 (45.4)	12 (26.1)	0.2147
Further cancers-precancerous lesions (%)	1 (9.1)	9 (19.6)	0.4244
PI-based ART (%)	7 (63.6)	25 (54.3)	0.5783
Median interval (IQR days)			
HIV diagnosis-ART	31 (0-365)	16.5 (0-55.25)	0.522
HIV-KS diagnosis	26 (3.5-125.75)	0.5 (0-235.25)	0.5272
Already on ART at KS diagnosis (%)	4 (36.4)	13 (28.3)	0.5989

*expressed as cells/µl; **expressed as copies/ml

Univariate analysis did not show any statistically relevant risk factor influencing mortality.

Discussion. This study, carried out in 2 Italian hospitals, confirmed that KS is not a rare disease among PLWH, as shown in the 2020 report, too[1,6,7] and its frequency has remained constant through the years. Literature enlightened male gender, homosexual behavior, and sub-Saharan and Mediterranean origin being KS risk factors in PLWH.[2-5] Similarly, in our study, males and MSM were the most affected population groups, while Africans were a minority in our sample. This distribution reflects the characteristics of patients observed in our centers, mostly males, Italians, and MSM, as shown in previous publications.[8-10] The burden of risk factors changes in different settings; in sub-Saharan Africa, male predominance in KS is less pronounced, while extremely relevant is a history of sexually transmitted infections (STIs).[5,11] Concerning STIs, only 11.7% of our cases were co-infected with HBV and HCV, and they did not show a higher mortality rate. Also, HPV infection and smoking regarded just a minority of our population and did not result to be negative prognostic factors in this analysis. Unfortunately, too many patients were not tested for HPV and were not asked about their smoking attitude.

Previously it has been demonstrated that high viral load, low nadir CD4 count, and CD4/CD8 ratio were associated with KS occurrence.[3,4,12] More than 70% of our patients had a CD4 count <350 cells/µl either at HIV or at KS diagnosis, and the median value of CD4 nadir was 63 cells/µl. Similar frequency for viral load and CD4/CD8 ratio. None of these immunological and viral parameters resulted in enhancing mortality rate in our sample. Low CD4 cell quantity and high frequency of concomitant diagnosis of HIV infection and KS confirmed the increasing number of late HIV diagnoses reported by Istituto Superiore di Sanità.[13]

Cutaneous and disseminated forms were the most common in this study, while mucosal ones were localized in the oral cavity except in 2 cases: 1 in the anus and 1 in the ocular conjunctive. Rohrmus B et al. reported a higher death rate in oral KS than in cutaneous KS.[14] Our 5 cases of oral KS are too few to make the same comparison, and our analysis focused on disseminated versus not disseminated KS finding no difference in mortality rate. In addition, 12 KS patients also had other cancerous or precancerous lesions. In particular, 3 were affected by other HHV-8-related neoplasms: 2 by Castleman disease and 1 by primitive effusive Lymphoma. Unfortunately, KS diagnosis was supported by positive HHV-8 viremia and histology only in 15 and 6 individuals, respectively. All the 5 persons having negative HHV-8 viremia were affected by cutaneous KS.

Except for 3 individuals whose data were unavailable, every patient received ART, and 18, mostly with disseminated KS, required chemotherapy, too. PI

was often included in the ART regimen according to the evidence of some literature[15,16]. However, there is still debate about this aspect,[17] and also our study failed to prove any benefit of PI-based ART on mortality rate.

Finally, it is worth noticing that KS diagnosis occurred after HIV diagnosis in 21 patients, and 17 were already on ART when KS was discovered. This late diagnosis of patients on ART therapy is unsurprising because an increase of KS incidence in the first 6 months of ART has been estimated to coincide with the immune reconstitution.[18,19] In our sample, the 17 patients with a new diagnosis of KS had been on treatment for about 200 days. This, together with an uncertain adherence, could explain why, despite therapy, 52.9% of them did not reach viral suppression at KS diagnosis. Moreover, the main characteristic of this particular group of PLWH was the longer median interval between HIV diagnosis and ART starting (1500 versus 17 days) due to the higher CD4 count (median CD4 nadir 123 versus 63 cells/µl), and this aspect could represent an additional risk factor for KS.[5]

ART advent and its early starting significantly lowered KS occurrence.[3,4,20] However, our analysis did not show relevant differences in HIV diagnosis-ART starting interval between dead and alive groups.

Limitations of this study are the small sample size, the number of people lost to follow-up, and missing data due to the retrospective nature of this work.

Conclusions. Despite the ART era, KS is not a rare disease and keeps high lethality. Individuals examined in our study were mostly Italians, MSM, with high HIV viral load, low CD4 count and CD4/CD8 ratio. Most of them were affected by cutaneous KS and treated with PI-based ART. Analyzing epidemiological and clinical aspects, immune and viral parameters, and type and timing of ART, we did not find any statistically relevant risk factor influencing mortality rate. However, the sample size is too small to generalize these results, and further studies may be needed.

Chiara Papalini[1], Lucia Brescini[2], Laura Curci[1], Sabrina Bastianelli[1], Francesco Barchiesi[2], Andrea Giacometti[2] and Daniela Francisci[1].

[1] Infectious Diseases Clinic, Santa Maria della Misericordia Hospital, Università degli Studi di Perugia, Perugia, Italy.
[2] Biomedical Sciences and Public Health Department, Università Politecnica delle Marche, Ancona, Italy.

Competing interests: The authors declare no conflict of Interest.

Correspondence to: Chiara Papalini. Infectious Diseases Clinic, Santa Maria della Misericordia Hospital, Sant'Andrea delle Fratte, 06129 Perugia, Italy. Tel.:+390755784375, Fax: +390755784346. E-mail: chiara.papalini@ospedale.perugia.it chiara.papalini@studenti.unipg.it

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