A clinical study of Kaposi Sarcoma among HIV/AIDS patients in Albania

Erjona Shehu[1], Esmeralda Meta[2], Arsilda Gjataj[2], Ermira Vasili[1], Dhimiter Kraja[2], Arjan Harxhi[2]

[1]Service of Dermatology, University Hospital Centre "Mother Teresa", Tirana, Albania;
[2]Service of Infectious Disease, University Hospital Centre "Mother Teresa", Tirana, Albania.

Corresponding author: Erjona Shehu
Address: Rr. Dibres, No. 372, Tirana, Albania;
Telephone: 0682257750; E-mail: erjonashehu@yahoo.com

Abstract

Aim: This descriptive study aims to characterize the epidemiological and clinical features of Kaposi Sarcoma (KS) among HIV/AIDS patients in Albania.
Methods: This is an observational retrospective study of 32 adult patients diagnosed with AIDS-associated Kaposi's sarcoma between January 2007 to December 2015 at the Ambulatory HIV/AIDS Clinic, Infectious Disease Service, University Hospital Centre of Tirana.
Results: The median age at diagnosis was 43 years (range: 26-79 years), with HIV-KS cases more common among patients of age 41-50 years (32%). Men comprised 91% of the study population, while men who had sex with men comprised 12% of the cases. The most common lesions of the KS in AIDS patients were the nodule (46%), patch (31%) and plaque (15%). The most common tumour locations were the trunk (47%), lower extremity (36%), oral (34%) and face (28%). The most common oral lesions were nodule (54%) and exophytic (36%). 24 patients (75%) had T0 stage of the disease, while 8 cases (25%) had T1 stage of the disease. The median CD4 level at baseline was 142 cell/mm^3. All the cases were treated with combined antiretroviral therapy (ART). The most used ART regimens were zidovudine + lamivudine + efavirenz. Seven patients (22%) received chemotherapy. Mortality rate during the study period was 22%.
Conclusion: In more than two thirds of the cases (69%), the diagnosis of KS was the HIV/AIDS presenting or defining illness/diagnosis, which indicates a very late HIV diagnosis in Albania.

Keywords: ART, HIV/AIDS infection, Kaposi Sarcoma.

Introduction

Kaposi's sarcoma (KS) is the most common malignancy seen in the setting of HIV infection. In the current era of treatment, KS is generally identified as a late manifestation of HIV infection, occurring when immunosuppression is severe (1). Treatment with effective antiretroviral therapy (ART) has led to a dramatic decline in KS incidence. A prescription for ART may reduce the likelihood of KS by 50% (2). In a multivariate analysis, the Multicentre AIDS Cohort Study demonstrated an 81% reduced risk of death for KS patients treated with combination ART (3). Although Albania is considered a low prevalence country for HIV infection, reported cases are increasing every year. Until December 2015 there are 870 HIV cases reported in Albania, with 87 cases reported during 2015, where more than half of them were at AIDS stage (4). The ART was introduced in 2004 in Albania, with currently more than 450 cases being under treatment at Infectious Disease (ID) Service and ID Paediatric Service at University Hospital Centre of Tirana (UHCT).

This is the first study carried out in Albania which aims to characterize the epidemiological and clinical features of KS and HIV/AIDS patients followed at Ambulatory HIV Clinic at Infectious Disease (ID) Service, University Hospital Centre of Tirana (UHCT) "Mother Teresa".

Methods

This is an observational retrospective study conducted at the Ambulatory HIV/AIDS Clinic, Infectious Disease Service, University Hospital Centre of Tirana. This is the only centre in Albania which provides care and treatment for all HIV infected adult patients since 2007. In order to select the patients included in the study, we reviewed the database of the HIV cohort adult patients who are receiving care and are followed at the Ambulatory HIV clinic from January 2007 to December 2015. There were 429 adult patients with HIV diagnosis whose data were available. The study population consisted of all HIV adult patients diagnosed with Kaposi Sarcoma, either by clinical or histological diagnosis. In the database, there were 32 cases with KS diagnosed clinically or histologically which were included in our study. For the purpose of this analysis, a KS diagnosis was defined by the presence of a clinical-only diagnosis of KS, or a clinical KS diagnosis accompanied by definitive or indeterminate pathologic confirmation. Patients with a clinical diagnosis and a negative biopsy were not considered to have KS.

Information obtained included patient's age, gender, risk of HIV transmission, time of KS diagnosis related to HIV diagnosis, CD4 cell count at time of HIV diagnosis and when HIV-KS was diagnosed, other HIV associated opportunistic diseases, general area of KS lesion, tumour localization, type of lesion, oral involvement, antiretroviral treatment regimens, and systemic chemotherapy. KS stage was defined per AIDS clinical trials group (ACTG) tumour staging classification as T0 if disease was confined to the skin and/or lymph nodes or oral involvement was confined to the hard palate, or T1 if there was pulmonary or gastrointestinal involvement, tumour associated oedema or ulceration, or extensive oral involvement.

Results

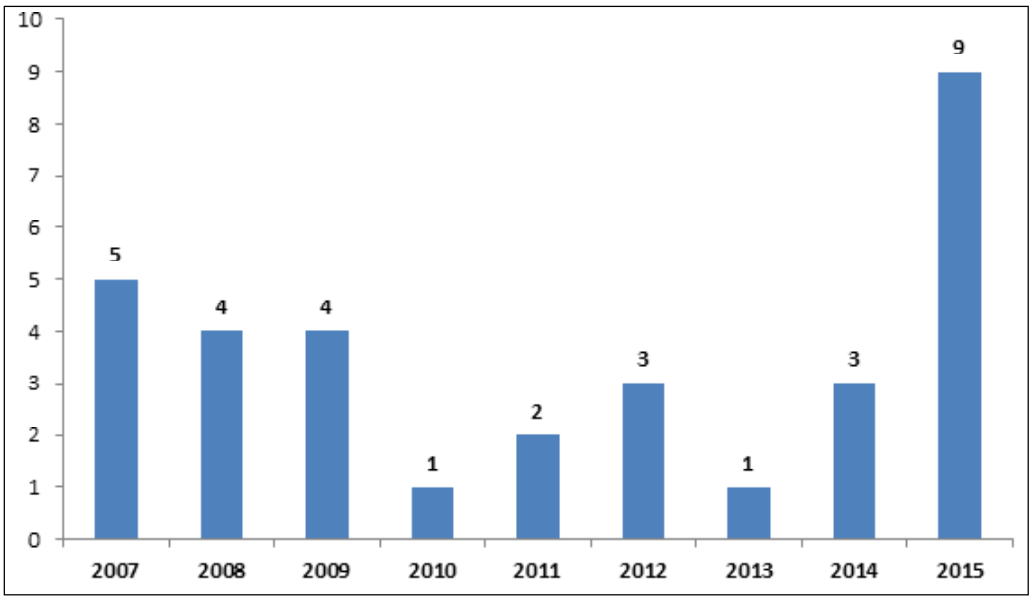
This study comprised 32 patients diagnosed with HIV related KS (Table 1). In majority of cases (22 cases, 69%), diagnosis of KS was the first HIV/AIDS presenting or defining illness/diagnosis. For those KS cases diagnosed after HIV diagnosis being established, the median time of diagnosis of KS was 4.3 years (range 0.8-15 years). Diagnosis of KS was clinically based in 24 cases (75%) and histopathologically based in 8 cases (25%). Number of KS cases diagnosed among HIV patients at our Service each year is shown in Figure 1, with the highest number diagnosed during 2015. The median age at the time of KS diagnosis was 43 years (range = 26-79), with HIV-KS cases more common among patients of age 41-50 years (32%). Men compri-

sed 91% of the study population with male to female ratio was 9:1, while those who declared as men who have sex with men comprised 12% of cases.

Table 1. Epidemiological characteristics of the patients

Characteristics	Numbers (Percentages)
Number of patients	32
Male	29 (91%)
Female	3 (9%)
Age (mean years)	43
<30 years	8 (25%)
31-40 years	61 (8%)
41-50 years	10 (32%)
>51 years	8 (25%)
Civil and risk status (n=27)	
Married	16 (48%)
Single	7 (21%)
Divorced	2 (6%)
MSM	4 (12%)
Number of patients with concomitant HIV-KS diagnosis	22 (69%)
Number of patients with KS diagnosed after HIV diagnosis	10 (31%)
Time from HIV to KS diagnosis, mean (range)	4.3 years (1-15 years)

Figure 1. Number of new AIDS-KS cases by year



Clinical characteristics of the patients are summarized in Table 2. The most common lesions of the KS in AIDS patients are the nodule (46%), patch (31%) and plaque (15%). The most common tumour locations were the trunk (47%), lower extremity (36%), oral (34%) and face (28%). The most common oral lesions were nodule (54%) and exophytic (36%) with palate and tongue as the

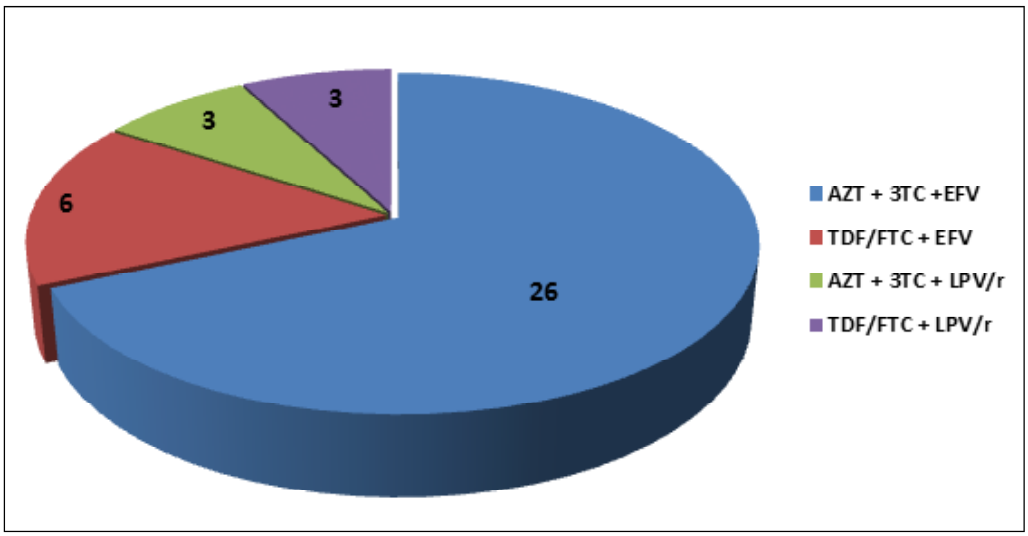
most common site location. 24 patients (75%) had T0 stage of the disease, while 8 cases (25%) had T1 stage of the disease (7 cases with extensive oral involvement and 1 case with visceral and oral involvement). About one third of cases presented with anaemia, leukopenia and thrombocytopenia. The median CD4 level at baseline was 142 cell/mm^3 (range 7- 530 cells). The most common concomitant opportunistic infections were wasting syndrome (59%), oral-pharyngeal candidiasis (50%), pneumonia (34%), syphilis (17%), and dermatitis (13%).

Table 2. The clinical characteristics of AIDS-KS cases

Characteristics	Numbers (Percentages)
Average CD4+ T-cell count at KS diagnosis (cell/mm^3) (range)	142 cell/mm^3, (7-530)
Type of lesions	
Patch	8 (31%)
Plaque	4 (15%)
Nodule	12 (46%)
Edema	1 (4%)
Erosion	1 (4%)
Tumor localization	
Upper extremity	7 (22%)
Lower extremity	12 (36%)
Upper and lower extremity	8 (24%)
Trunk	15 (47%)
Face	9 (28%)
Oral (+ skin)	11 (34%)
Oral type: Nodule	6 (55%)
Exophytic	4 (36%)
Patch	3 (27%)
Oral site: Gingival	3 (27%)
Tongue	4 (36%)
Palatum	6 (55%)
Visceral	1 (3%)
Prognosis (mortality)	5 (16%)
Anemia	9 (28%)
Leukopenia	10 (31%)
Thrombocytopenia	9 (28%)
Other concomitant OI	
Oro-pharyngeal candidiasis	16 (50%)
Pneumonia	11 (34%)
Wasting syndrome	19 (59%)
Syphilis	5 (17%)
Genital warts	5 (17%)
Dermatitis atopic	4 (13%)

All cases were treated with combined antiretroviral therapy (ART) (Figure 2). 25 patients (78%) with KS were under first line ART therapy while less than a quarter of cases (7 cases, 22%) have been prescribed second line regimens. The most used ART regimens were zidovudine + lamivudine + efavirenz (81%) and then TFD/FTC/EFV (18%). Seven patients (22%) received chemotherapy, which was based on doxorubicin regimen in the majority of time. The median time of follow up was 3.97 years (range 0.3 to 11 years). Mortality rate during the study period was 22% (7 patients died).

Figure 2. ART regimens



Discussion

The estimated prevalence of HIV-associated KS at our cohort of HIV patients was about 7.5%. At the beginning of the HIV epidemic, Kaposi sarcoma was one of the most common manifestations of AIDS (5), present during the mid-1980s in 25% of individuals at the time of AIDS diagnosis in the United States, but decreased steadily through the late 1980s and mid-1990s, down to 2% after the advent and widespread use of highly active antiretroviral therapy (HAART) in 1996 (6). Most of HIV-KS cases at our Service are diagnosed clinically, due to limited diagnostic pathology availability especially for this type of patients at our facility. Skin punch biopsy and histological examination was performed in 8 cases (25%). All the eight cases with confirmed histological diagnoses were diagnosed very recently during year 2015. There is discrepancy in the data regarding high proportion of male gender (91%) and low proportion of MSM risk group (12%) which underscores the low level of sexual orientation disclosure among HIV male patients and under-reporting phenomenon of this risk behaviour in Albania. According to the Institute of Public Health in Tirana, MSM route of transmission is reported to be around 11% for 2015, while other neighbouring countries report rates of 40 to 60% (7). Different cohorts of HIV patients in North America and Europe have revealed an elevated prevalence of HIV associated KS in men who have sex with men, which goes till 90% of cases (8,9). In more than two third of the cases (69%) the diagnosis of KS was the HIV/AIDS presenting or defining illness/diagnosis which indicates a very late HIV diagnosis in Albania. This is also confirmed by the fact of very low average CD4 level at HIV-KS diagnosis time. Late HIV diagnosis is common

in Albania, with 75% of patients being diagnosed with a CD4 count <350 cells/mm^3 and 52% with a CD4 counts <200 cells/mm^3, representing severe immunosuppression (7). The data from our study, together with late HIV diagnoses trends in Albania, indicates that a large proportion of Albania's HIV population are not being tested and diagnosed promptly and suggests a relatively large undiagnosed population within the country.

The clinical characteristics of KS lesions of our cases were an early patch and late stage nodule. The most common locations of the lesions were the trunk and the lower extremities. In more than two third of cases there was an oral cavity location of the lesions, with hard palate, gingiva and dorsum of the tongue as the most commonly affected sites. It has been reported that in 22% of HIV-seropositive subjects with KS, the initial presentation of HIV-KS is in the mouth, and that in up to 70% of subjects with HIV-KS, the mouth will sooner or later be affected (10,11). All patients in our study received ART while only one fifth received chemotherapy. While HAART is recommended for virtually all patients with a KS diagnosis, individuals with advanced and/or symptomatic KS should receive some form of local or systemic therapy specific for KS (12). Any therapeutic choice for treatment of patients with AIDS and KS in the HAART era should take into consideration several parameters, such as the extension of mucous-cutaneous KS lesions, the presence of visceral involvement that may be life-threatening (e.g., symptomatic lung KS), KS involvement at a location that could compromise a specific organ function, and the intensity of immunosuppression (13).

Furthermore, regression with cART alone has been well-documented, and a pooled analysis of patients with early disease (T0 = KS with low tumour volume, no associated ulceration or oedema, and no visceral disease) who had not received cART previously suggest that approximately 80% will have disease regression with cART alone, with median time to response ranging from 3-9 months (14). Several modalities, including radiotherapy, topical therapy, cryotherapy, or intralesional injection historically have been employed for control of localized KS, but their use has been largely replaced by cART. However, systemic therapy remains indicated for the bulky, rapidly progressing, symptomatic, or life-threatening disease (14). The most common chemotherapy used among our cases was doxorubicin. Also the literature data shows that liposomal doxorubicin is currently the chemotherapeutic agent of choice for advanced KS (15). In a study of moderate to advanced KS, those receiving liposomal doxorubicin in addition to ART had a markedly better response rate at 48 months than did those on ART alone (76 versus 20%) (16). Majority of our patients (81%) were under non-nucleoside based ART regimens, which is according to the National Guidelines for ART (Albanian Guideline 2006). Effective combination of antiretroviral therapy consists of a combination of either a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) with two nucleoside reverse transcriptase inhibitors (NRTI). In the Chelsea and Westminster Cohort of 8640 patients with HIV, 1240 patients with KS were identified, and NNRTI and PI based regimens had the same protective effect against the development of KS (17).

In summary, we found that the number of cases of HIV-associated KS being diagnosed yearly in Albania is increasing, especially among middle-aged male patients. KS remains an important clinical problem in terms of early diagnosis and management in Albania.

Conflicts of interest: None declared.

References

1. Von Roenn JH. Treatment of HIV-associated Kaposi Sarkoma. Northwestern University, HIV InSite; 2003. Available from: http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-06-02-04 (Accessed: March 20, 2016).

2. Jones JL, Hanson DL, Dworkin MS, Jaffe HW. Incidence and trends in Kaposi's sarcoma in the era of effective antiretroviral therapy. J Acquir Immune Defic Syndr 2000;24:270-4.

3. Piedbois P, Frikha H, Martin L, Levy E, Haddad E, Le Bourgeois JP. Radiotherapy in the management of epidemic Kaposi's sarcoma. Int J Radiat Oncol Biol Phys 1994;30:1207-11.

4. Institute of Public Health. HIV/ AIDS in Albania. Tirana; 2015.

5. Biggar RJ, Rosenberg PS, Cote T. Kaposi's sarcoma and non-Hodgkin's lymphoma following the diagnosis of AIDS. Multistate AIDS/ Cancer Match Study Group. Int J Cancer 1996;68:754-8.

6. Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. AIDS 2006;20:1645-54.

7. World Health Organization. HIV in Albania: An epidemiological review. WHO Europe, 2015. Available from: http://www.euro.who.int/en/health-topics/communicable-diseases/hivaids/publications/2015/hiv-in-albania-an-epidemiological-review-2015 (Accessed: March 20, 2016).

8. Nguyen HQ, Magaret AS, Kitahata MM, Van Rompaey SE, Wald A, Casper C. Persistent Kaposi sarcoma in the era of highly active antiretroviral therapy: characterizing the predictors of clinical response. AIDS 2008;22:937-45.

9. La Ferla L, Pinzone MR, Nunnari G, Martellotta F, Lleshi A, Tirelli U, et al. Kaposi's sarcoma in HIV-positive patients: the state of art in the HAART-era. Eur Rev Med Pharmacol Sci 2013;17:2354-65.

10. Hille JJ, Webster-Cyriaque J, Palefski JM, Raab-Traub N. Mechanisms of expression of HHV8, EBV and HPV in selected HIV-associated oral lesions. Oral Dis 2002;8:161-8.

11. Epstein JB, Cabay RJ, Glick M. Oral malignancies in HIV disease: changes in disease presentation, increasing understanding of molecular pathogenesis, and current management. Oral Surg Oral Med Oral Pathol 2005;100:571-8.

12. Kaplan LD. HIV-associated Neoplasia. In: Volberding PA, Sande MA, Greene WC, Lange JMA (Eds). Global HIV Medicine. Elsevier 2008:463-74.

13. Dupin N, Del Giudice P. Treatment of Kaposi Sarcoma in the Highly Active Antiretroviral Therapy Era. Clin Infect Dis 2008:47;418-20.

14. Krown SE. Highly active antiretroviral therapy in AIDS-associated Kaposi's sarcoma: implications for the design of therapeutic trials in patients with advanced, symptomatic Kaposi's sarcoma. J Clin Oncol 2004;22:399-402.

15. Uldrick, TS, Whitby D. Update on KSHV epidemiology, Kaposi Sarcoma pathogenesis, and treatment of Kaposi Sarcoma. Cancer Lett 2011;305:150-62.

16. Martín-Carbonero L, Barrios A, Saballs P, Sirera G, Santos J, Palacios R, et al. Pegylated liposomal doxorubicin plus HAART versus HAART alone in HIV patients with Kaposi's Sarcoma. AIDS 2004;18:1737-40.

17. Portsmouth S, Stebbing J, Gill J, Mandalia S, Bower M, Nelson M, et al. A comparison of regimens based on non-nucleoside reverse transcriptase inhibitors or protease inhibitors in preventing Kaposi's sarcoma. AIDS 2003;17:F17-22.