JPDS Journal of the Philippine Dermatological Society

CASE SERIES

AIDS-associated Kaposi sarcoma: A case series in the Philippine setting

Ricky H Hipolito, MD, FPDS,[1] Ma Teresita G Gabriel, MD, FPDS,[1]
Johannes F Dayrit, MD, FPDS, FDSP,[1] Ma Carmela P Bucoy, MD[1]

ABSTRACT

INTRODUCTION Acquired immunodeficiency syndrome-Kaposi sarcoma (AIDS-KS) has unique clinical characteristics, often disseminated on presentation, a rapidly progressive course, and often fatal outcome. Describing the epidemiology and clinical characteristics of AIDS-KS in the Philippines may lead to early recognition, diagnosis, and management of this condition, which are the keys to preventing significant complications.

CASE SERIES AIDS-KS in 11 Filipino MSM patients with a mean age of 36.55 years (SD 11.54) was described. Violaceous plaques and nodules were present for an average of 5.1 months prior to diagnosis confirmed by biopsy. Histopathologic findings from all patients were consistent with KS.

The median CD4+ count of patients was 44 cells/microliter (range, 4 to 181). Six patients presented with opportunistic infections (OI)/AIDS-related conditions (ARC). The most common OIs observed were pulmonary tuberculosis, oropharyngeal candidiasis, and Pneumocystis jiroveci pneumonia. Nine patients improved with highly active antiretroviral therapy (HAART). One patient required modification on his HAART regimen, which was shifted to 2 NRTI and ritonavir-boosted protease inhibitor, and one patient died due to AIDS-related complications.

CONCLUSION This series of 11 cases of AIDS-KS showed similar demographic, clinical and histopathologic characteristics to previously published studies. Findings suggest the need for earlier recognition and diagnosis. While HAART afforded clinical improvement in a majority of patients, other treatment options such as chemotherapy should be considered for appropriate patients.

KEYWORDS Kaposi sarcoma, AIDS-KS, HAART

INTRODUCTION

Kaposi sarcoma (KS) is the second most frequent tumor occurring in patients with acquired immunodeficiency syndrome (AIDS) particularly in men who have sex with men (MSM).1 A second infectious etiology, transmitted primarily through saliva was identified: the Kaposi sarcoma-related herpes virus (KSHV).[1]

AIDS-KS has been recognized as a distinct class of Kaposi sarcoma due to its unique epidemiologic and clinical characteristics. It has a predisposition towards MSM-human immunodeficiency virus (HIV)-positive homosexuals, often disseminated at presentation, rapidly progressive and often fatal.[1]

The availability of combination antiretroviral treatment (cART) was accompanied by a significant decline in the incidence of AIDS-KS, with an estimated occurrence of 900 per year in the United States.[1]

The Philippines, with a 174% increase in HIV incidence between 2010 and 2017, has the fastest growing HIV epidemic in the world.[2] The great majority are MSM (87%); therefore, AIDS-KS may become a more significant problem in the future as people living with HIV/AIDS (PLHIV) are aging and the disproportionate prevalence of the epidemic among MSM.[1]

Despite being one of the first AIDS-defining illnesses recognized, there is still a paucity of published studies on the prevalence, clinical characteristics, and management of AIDS-KS in the local setting.

This report aimed to describe the epidemiologic, clinical and histopathologic characteristics of AIDS-KS patients seen at a tertiary referral center. It also aimed to determine the management and outcomes of the patients. This report can facilitate early recognition of AIDS-KS with appropriate treatment leading to less deformity

[1]Department of Dermatology, Research Institute for Tropical Medicine, Alabang, Muntinlupa, Philippines

Corresponding author
Ricky H. Hipolito, MD, FPDS

Conflict of interest
None

Source of funding
None

and other complications. It can also serve as basis for further studies on AIDS-KS which can pave the way for better therapeutic strategies.

CASE SERIES

A retrospective review was done among patients of the Research Institute for Tropical Medicine (RITM) Department of Dermatology, a tertiary referral center in Infectious Disease and Dermatology. This review included 11 patients with HIV and histopathologically confirmed AIDS-KS from 2012 to 2018 (Table 1). We reviewed the medical records, clinical photographs, and histopathologic slides, which were read by the department dermatopathologist.

All patients were Filipino MSM with a mean age of 36.55 years (SD 11.54) (range, 23 to 58). The mean duration of skin manifestations to diagnosis was 5.1 months (SD 6.6) (range, 1 to 24). All patients presented with violaceous plaques and nodules. Skin biopsy specimens stained with hematoxylin and eo-

Table 1. Clinical characteristics of patients

Patient	Age	Sex	Lesion	Duration (months)	Distribution	Initial CD4+ Count	Histopathology findings	Opportunistic infection / AIDS-related Conditions	HAART
1	35	M	Violaceous Plaques, Nodules	1	Chest, arms, axillae, palate (+ oral lesions)	154	Acanthosis; basal cell layer hyperpigmentation; mixed inflammatory infiltrate; slit-like vessels; spindle shaped cells; promontory sign; red blood cell extravasation	None	Lamivudine Zidovudine Tenofovir
2	33	M	Violaceous plaques	24	Back, left thigh, extremities	181	Acanthosis; basal cell layer hyperpigmentation; slit-like vessels; spindle-shaped cells; capillary proliferation; red blood cell extravasation	None	Lamivudine Zidovudine Nevirapine
3	29	M	Violaceous plaques, nodules	2	Face, trunk, back, upper extremities, lower extremities, left sole (+ oral lesions)	77	Acanthosis; slit-like vessels; spindle-shaped cells; promontory sign; red blood cell extravasation	Chronic diarrhea, Mycobacterium tuberculosis, *Pneumocystis jirovecci* pneumonia	Lamivudine Zidovudine Efavirenz
4	48	M	Violaceous papules	2	Neck	41	Acanthosis; basal cell layer hyperpigmentation; slit-like vessels; spindle shaped cells; red blood cell extravasation	Recurrent pneumonia	Lamivudine Zidovudine Efavirenz
5	29	M	Violaceous plaques	1	Face and scalp	73	Mixed inflammatory infiltrate; slit-like vessels; spindle shaped cells; promontory sign	Oropharyngeal candidiasis	Lamivudine Zidovudine Efavirenz
6	25	M	Hyperpigmented plaques on face and scalp	4	Scalp, face and trunk	4	Mixed inflammatory infiltrate; slit-like vessels; spindle shaped cells; promontory sign; red blood cell extravasation	CMV retinitis, multi-drug-resistant pulmonary tuberculosis, oropharyngeal candidiasis	Lamivudine Zidovudine Efavirenz
7	48	M	Plaques and nodules	7	Face, trunk, extremities, (+ oral lesions)	10	Acanthosis; basal cell layer hyperpigmentation; mixed inflammatory infiltrate; slit-like vessels; spindle shaped cells	Multidrug-resistant pulmonary tuberculosis, oropharyngeal candidiasis	Lamivudine Zidovudine Efavirenz
8	23	M	Violaceous nodules and plaques	4	Trunk and extremities (2 mos. after HIV diagnosis)	30	Slit-like vessels; spindle-shaped cells; capillary proliferation, promontory sign, red blood cell extravasation	None	Lamivudine Zidovudine Tenofovir
9	46	M	Violaceous papules and plaques	4	Face, neck, trunk (+ oral lesions) (3 mos after HIV diagnosis)	44	Acanthosis; basal cell layer hyperpigmentation; slit-like vessels; spindle-shaped cells; red blood cell extravasation	Pulmonary tuberculosis	Lamivudine Zidovudine Tenofovir
10	28	M	Violaceous papules, plaques and nodules	1	Trunk, upper and lower extremities	28	Acanthosis, mixed inflammatory infiltrates; spindle-shaped cells; slit-like vessels; capillary proliferation, promontory sign	None	Lamivudine Zidovudine Efavirenz
11	58	M	Violaceous nodules	6	Trunk and extremities	73	Acanthosis; basal cell layer hyperpigmenation; mixed inflammatory infiltrate; spindle-shaped cells;	None	Lamivudine Tenofovir to Lamivudine Zidovudine Lopinavir/ritonavir

HAART=Highly active antiretroviral therapy; CMV=Cytomegalovirus

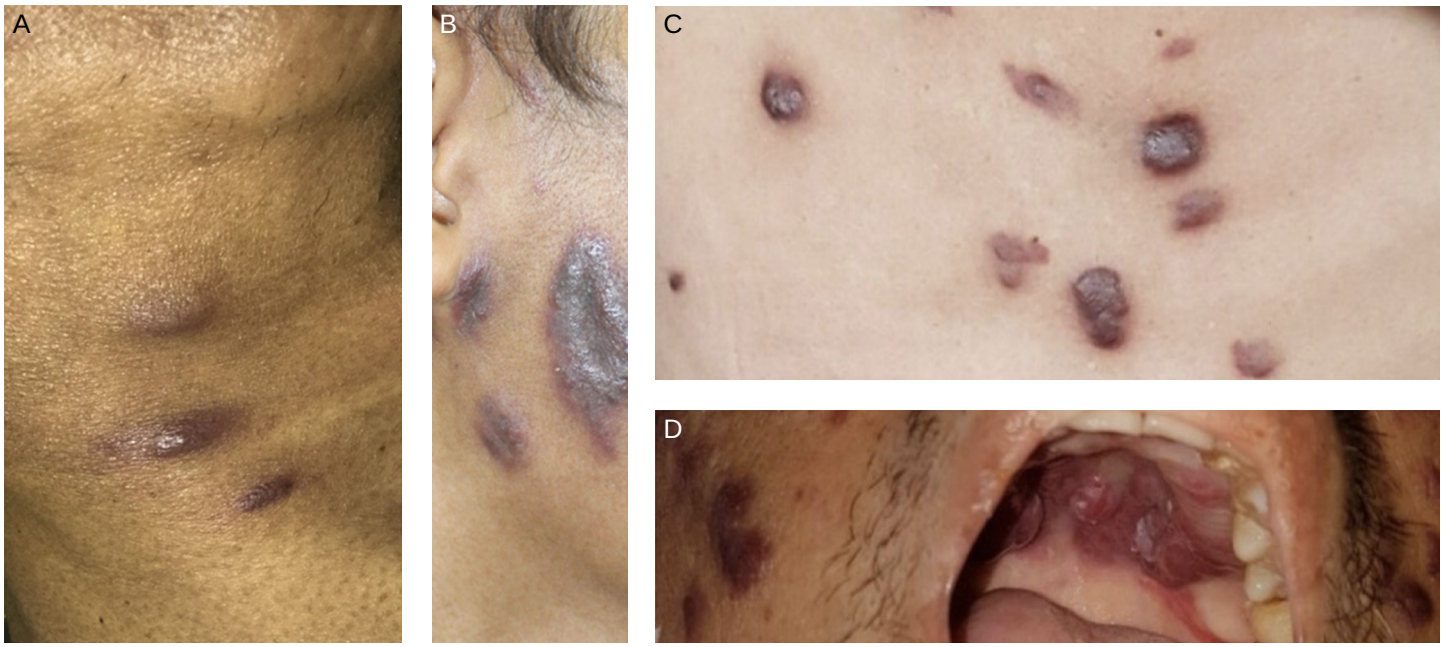

Figure 1. A and B. A 29-year-old man presenting with violaceous plaques and nodules distributed face and oral mucosa. **C and D.** A known case of HIV since 2016 and presented with a 4-month history of a solitary violaceous macule on the left side of the neck evolving into nodules and plaques with subsequent affectation of the retroauricular area, scalp, and face.

sin were obtained from all patients. Ancillary procedures such as chest x-ray, colonoscopy, chest/abdominal CT scan were done depending on clinical criteria.

The majority of patients (9/11) presented with widespread skin involvement. The skin lesions were noted on the trunk in 9/11 patients (Figure 1), upper and lower extremities in 8, face in 6, head and neck in 4 patients (Figure 2 B-D). Four patients presented with oral lesions (Figure 2 A). The median CD4+ count of patients was 44 cells/μL (range, 4 to 181). Six of 11 patients, whose CD4+ counts were between 4 to 77 cells/μL, presented with opportunistic infections (OI) /AIDS-related conditions (ARC). The most common OI observed were pulmonary tuberculosis (4/11), oropharyngeal candidiasis (3/11), and Pneumocystis jiroveci pneumonia (2/11). The other OI and ARC seen were chronic diarrhea, Cytomegalovirus (CMV) retinitis, anemia and AIDS wasting syndrome.

The histopathologic findings from all patients were consistent with KS (Figure 3A-B). The most common findings were spindle-shaped cells (11/11), slit-like vessels (10/11) and promontory sign (6/11). Other histologic features noted were red blood cell extravasation, inflammatory infiltrate, and capillary proliferation.

All patients were started on highly active antiretroviral therapy (HAART) with a combination of 2 nucleoside reverse transcriptase inhibitor (NRTI) and 1 non-nucleoside reverse transcriptase inhibitor (NNRTI). One patient was later shifted to 2 NRTI and ritonavir-boosted protease inhibitor.

Nine of 11 patients did not develop new lesions upon starting HAART. Two patients were hospitalized, with one admitted due to Pneumocystis jiroveci pneumonia. He was discharged improved after 15 days and there was note of decreased thickness of lesions after 1 month of initiation of HAART. The other patient, however, succumbed on his second hospital day due to acute respiratory distress syndrome (ARDS).

DISCUSSION

This case series included all male patients with a mean age of 36 years. This is consistent with a previous case series.[3] The mean duration prior to diagnosis of 5.1 months (SD 6.6) is corroborated by a previous report where almost half of the patients experienced a diagnostic delay of more than 3 months.[4] More than half of the patients had lesions for at least four months prior to diagnosis, which represents a significant diagnostic delay. A diagnostic lag of more than three months is proposed by some authors as a significant diagnostic delay as it is associated with a poor-risk stage AIDS-KS at presentation.[4] In a previous study, lack of pain, financial difficulties and distance to health care facility were the most common reasons found for delay in diagnosis.[4]

Widespread skin involvement is consistent with the rapidly progressive clinical characteristic of AIDS-KS.[5] Mucocutaneous involvement is usually located in skin of the lower extremities, face, trunk, genitalia and oropharyngeal mucosa.[6]

While most physicians expect AIDS-KS to present in the

JPDS
Journal of the Philippine Dermatological Society

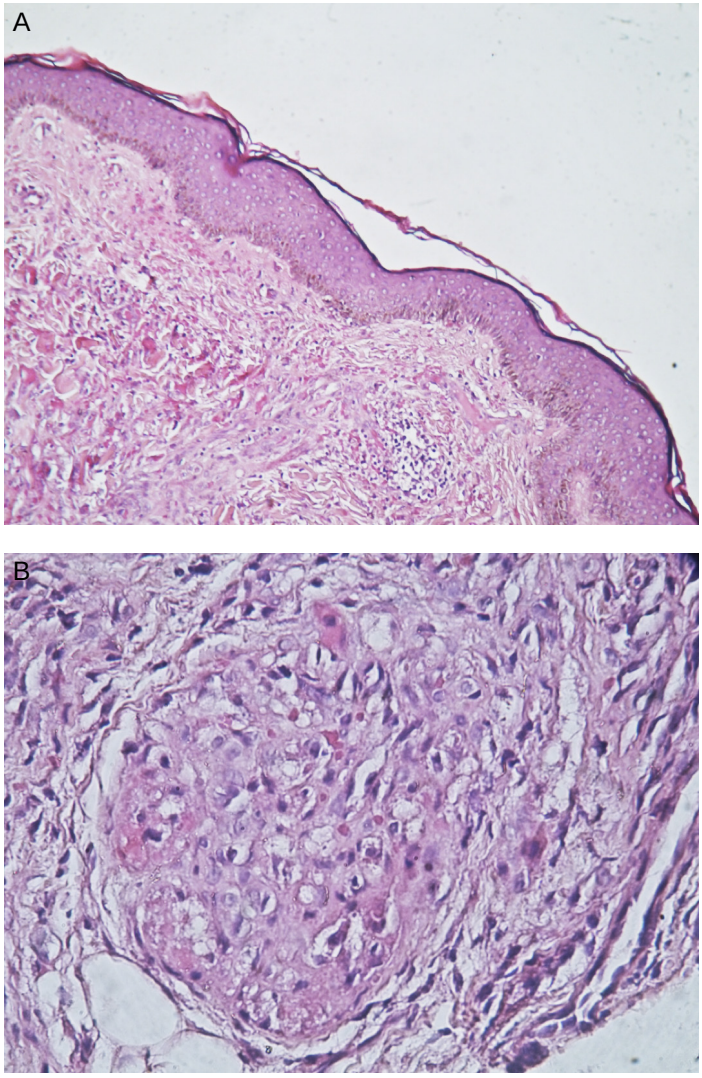

Figure 2. A and B. Sections showing spindle-shaped cells with basophilic nuclei and eosinophilic cytoplasm surrounding vessels. No mitotic figures seen.

late stages of AIDS, a recent study suggests AIDS-KS among patients with HIV and higher CD4+ cell counts is rising.[7] Thus, the index of suspicion should be high among patients with HIV patients and violaceous lesions even with a relatively high CD4+ cell count. Most patients in the series presented with widespread skin involvement and CD4+ count less than 150 cells/μL consistent with a previous series.[4] A significant association of OIs was found with CD4+ count less than 200 cells/μL, the most common being tuberculosis, candidiasis, and diarrhea.[8] This correlates with declining T helper function.[8]

Johnson et al. found in 2011 that Kaposi sarcoma can be a clinical challenge[7] and therefore recommended that biopsy be done in all patients with a high index of suspicion such as in homosexuals with HIV infection.[9] AIDS-KS histology is consistent with tumorigenesis in a background of chronic inflammation, immunosuppression and HIV-1 infection. Majority of KSHV-infected cells demonstrate a spindle morphology and presumed to have lymphatic origin.[10] KSHV establishes a lifelong infection to which the host response is chronic inflammation. In the background of immunosuppression, chronic inflammation can facilitate tumorigenesis. Chronic lymphedema, lymphangiogenesis induced by HIV-1 tat protein with the above factors lead to the development of slit like vessels and tumor formation.[11] The detection of human herpesvirus-8 (HHV-8) within KS lesional cells by using latency-associated nuclear antigen (LANA-1 or LNA-1) is the most useful diagnostic immunostaining method to differentiate KS from similar lesions.[8] AIDS-KS is characterized by its rapid course and frequent involvement of visceral organs at presentation.[1] In a published series, the stomach is the most frequent site affected.[3] The gastrointestinal tract, lymph nodes, and lungs are other commonly involved extracutaneous sites in AIDS-KS.[1]

It was found that among patients treated with HAART, those receiving efavirenz and protease inhibitor containing HAART regimen were 6.9 times (95% CI 1.8, 27, p = 0.006) and 14 times more likely (95% CI 1.8, 27, p = 0.006) to have lesion resolution compared to patients receiving stavudine, lamivudine, and nevirapine.[12] All patients in this series received either a protease inhibitor as part of their HAART regimen and/or efavirenz. Patients who had follow up information showed either stabilization of lesions or decrease in lesion size.[12] HAART works by immune reconstitution, decreased HIV-1 tat protein and decreased angiogenic cytokine production.[13]

A similar study was previously published which included six patients with AIDS-KS in a tertiary referral hospital in the Philippines.[14]

In a case series of 24 patients with AIDS-KS, two were successfully treated with HAART. Eighteen were given chemotherapy using adriamycin, bleomycin and vincristine (ABV). From those given ABV, remission was induced in 10 patients with a mean follow up time of 18.25 (±10.99) months while 3 died due to lesions in the lungs. Those who failed ABV treatment were given paclitaxel. Two patients achieved remission while another two died while on second-line chemotherapy.[15]

CONCLUSION

Eleven patients with AIDS-KS presented in this case series had similar demographic, clinical, and histopathologic characteristics as previously published studies. The need for early diagnosis through clinical suspicion and biopsy of lesions will ensure optimum outcome and quality of life of patients. HAART shows favourable outcomes in most cases of AIDS-KS. Other treatment options such as chemotherapy should be considered for appropriate patients.

REFERENCES

1. Gonçalves PH, Uldrick TS, & Yarchoan R. HIV-associated Kaposi sarcoma and related diseases. AIDS. 2017;31(14):1903-16. doi: 10.1097/QAD.0000000000001567.
2. Gangcuangco LMA. HIV crisis in the Philippines: urgent actions needed. Lancet Public Health. 2019 Feb;4(2):e84. doi: 10.1016/S2468-2667(18)30265-2. PMID: 30738505.
3. Pires CAA, Noronha MAN, Monteiro JCMS, Costa ALCD, Abreu Júnior JMC. Kaposi's sarcoma in persons living with HIV/AIDS: a case series in a tertiary referral hospital. An Bras Dermatol. 2018 Jul-Aug;93(4):524-8. doi: 10.1590/abd1806-4841.20186978. PMID: 30066758.
4. De Boer C, Niyonzima N, Orem J, Bartlett J, & Zafar SY. (2014). Prognosis and delay of diagnosis among Kaposi's sarcoma patients in Uganda: a cross-sectional study. Infect Agents Cancer. 2014;9;17. doi: 10.1186/1750-9378-9-17.
5. Mehta S, Garg A, Gupta LK, Mittal A, Khare AK, & Kuldeep CM. Kaposi's sarcoma as a presenting manifestation of HIV. Indian J Sex Transm Dis AIDS . 2011;32(2):108-10. doi: 10.4103/0253-7184.85415.
6. Pantanowitz L, & Dezube BJ. (Kaposi sarcoma in unusual locations. BMC Cancer. 2008;8:190. doi: 10.1186/1471-2407-8-190.
7. Crum-Cianflone NF, Hullsiek KH, Ganesan A, Weintrob A, Okulicz JF, Agan BK, & Infectious Disease Clinical Research Program HIV Working Group. Is Kaposi's sarcoma occurring at higher CD4 cell counts over the course of the HIV epidemic? AIDS. 2010;24(18):2881-3.
8. Damtie D, Yismaw G, Woldeyohannes D. Anagaw B. Common opportunistic infections and their CD4 cell correlates among HIV-infected patients attending at antiretroviral therapy clinic of Gondar University Hospital, Northwest Ethiopia. BMC Res Notes. 2013;6:534. doi: 10.1186/1756-0500-6-534.
9. Johnson EL, Pierpont YN, Donate G, Hiro MH, Mannari RJ, Strickland TJ, et al. Clinical challenge: cutaneous Kaposi's sarcoma of the lower extremity. Int Wound J. 2011;8:163-8. doi: 10.1111/j.1742-481X.2010.00763.x.
10. Radu O & Pantanowitz L. Kaposi Sarcoma. Arch Pathol Lab Med. 2013;137(2): 289-94. doi: 10.5858/arpa.2012-01010-RS.
11. Douglas JL, Gustin JK, Moses AV, Dezube BJ, & Pantanowitz L. Kaposi sarcoma pathogenesis: a triad of viral infection, oncogenesis and chronic inflammation. Transl Biomed. 2010;1(2):172.
12. Nguyen HQ, Okuku F, Ssewankambo F, Magaret AS, Johnston C, Wald A, et al. AIDS-associated Kaposi sarcoma in Uganda: response to treatment with highly active antiretroviral therapy and chemotherapy. Infect Agents Cancer. 2009;4(Suppl 2):O5. doi: 10.1186/1750-9378-4-S2-O5.
13. Stebbing J, Portsmouth S, Gazzard B. How does HAART lead to the resolution of Kaposi's sarcoma? J Antimicrob Chemother. 2003 May;51(5):1095-8. doi: 10.1093/jac/dkg199. PMID: 12668573.
14. Catedral L, Caro-Chang L, Tan HN, Velasco R Jr, King R, Ting, FI, et al. AIDS-related Kaposi sarcoma in a tertiary university hospital in Manila, Philippines: a report of six cases. Asian J Oncol. 2020;06. doi: 10.1055/s-0040-1713317.
15. Gwaram BA. Clinical presentation and treatment outcome of HIV associated Kaposi sarcoma in a tertiary health centre in Nigeria. J Med Res. 2016;2:110-3.