Short Report: Elevation of Soluble Intercellular Adhesion Molecule-1 Levels, but Not Angiopoietin 2, in the Plasma of Human Immunodeficiency Virus–Infected African Women with Clinical Kaposi Sarcoma

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Abstract. Circulating levels of endothelial activation biomarkers are elevated in during infection with human immunodeficiency virus 1 (HIV-1) and may also be increased in Kaposi sarcoma (KS). We compared 23 HIV-1-seropositive women with clinically diagnosed KS with 46 randomly selected controls matched for visit year, CD4 count, and antiretroviral therapy status. Conditional logistic regression was used to identify differences between cases and controls. The odds of clinical KS increased with increasing plasma viral load and with intercellular adhesion molecule 1 (ICAM-1) levels above or equal to the median. There was a borderline association between increasing plasma angiopoietin 2 levels and KS. In multivariable modeling including plasma viral load, angiopoietin 2, and ICAM-1, plasma ICAM-1 levels above or equal to the median remained associated with clinical KS (odds ratio = 14.2, 95% confidence interval = 2.3–87.7). Circulating ICAM-1 levels should be evaluated as a potential biomarker for disease progression and treatment response among HIV-infected KS patients.

Kaposi sarcoma (KS) is a multifocal vascular tumor composed of abnormally proliferating endothelial-like spindle cells.¹ KS tumors are of endothelial cell origin and express adhesion molecules known to attract leukocytes.² In addition, spindle cells express angiopoietins 1 and 2 (ANG-1 and ANG-2) and their cognate receptor, Tie-2.³ We have recently shown that plasma levels of endothelial activation biomarkers, including soluble intercellular adhesion molecule 1 (sICAM-1), vascular cell adhesion molecule 1 (sVCAM-1), and ANG-2, are increased during infection with human immunodeficiency virus 1 (HIV-1), and decrease after initiation of antiretroviral therapy (ART).^{4,5} Adhesion molecules, angiopoietins, and vascular growth factors may play a role in the development of KS, an important HIV-associated opportunistic malignancy common in settings in Africa.^{6–9}

We hypothesized that HIV-1-infected persons with clinical KS would have increased plasma levels of endothelial activation biomarkers (i.e., E-selectin, ICAM-1, VCAM-1, and vascular endothelial growth factor [VEGF]) and dysregulation of the ANG-1 to ANG-2 balance (i.e., lower ANG-1, higher ANG-2) than persons with no clinical evidence of KS. Our objective was to compare biomarker levels between cases with KS and controls with no evidence of KS.

Study participants were adult women enrolled in the Mombasa Cohort, a prospective study of high-risk women established in 1993 at the Ganjoni Municipal Communicable Disease Clinic in Mombasa, Kenya.¹⁰ We identified 23 HIV-1-seropositive women with clinically diagnosed KS, defined as typical, persistent cutaneous or oropharyngeal lesions ranging from flat pink or purplish patches to violaceous plaques or nodules noted at any visit after routine assessment began in 1999.¹¹

Plasma from cases was collected at the first visit on which clinical KS was noted. Plasma was not available from the

diagnosis visit for three cases. For these women, we identified a stored sample collected within six months of KS diagnosis. We randomly selected 46 HIV-1-seropositive controls with available plasma and no KS history, matched for visit year, CD4 count (within 100 cells/ μ L), and ART status. Three women were selected more than once as controls: two were selected twice, and one was selected three times, all at different visits.

At each monthly follow-up visit, women underwent a questionnaire on sexual behavior and recent symptoms, and a standardized physical examination during which lesions clinically compatible with oral or cutaneous KS were recorded.¹¹ All HIV-1-seropositive women provided quarterly blood samples for CD4 cell count determinations and storage of plasma. Participants received individualized risk-reduction counseling and free condoms at every visit. Treatment for sexually transmitted infections and HIV infections, including monitoring for disease progression and treatment of opportunistic infections, were provided free of charge. ART became available in 2004, after which treatment was offered to eligible women in accordance with Kenyan guidelines.

Quarterly CD4 counts were obtained by using a manual system (Cytosphere; Coulter, Hialeah, FL) during 1998–2004, and thereafter by using an automated method (FACSCount; Becton Dickinson, Franklin Lakes, NJ). Stored plasma samples were tested for HIV-1 RNA levels by using an HIV-1 viral load assay (Gen-Probe, San Diego, CA).¹² Levels of biomarkers, including ANG-1, ANG-2, E-selectin, ICAM-1, VCAM-1, and VEGF, were tested by using enzyme-linked immunoassays with validated specific matched capture and detection monoclonal antibody pairs (R&D Systems, Minneapolis, MN).

Descriptive statistics, including frequencies and medians with interquartile ranges, were used to describe characteristics of cases and controls. Conditional logistic regression analysis was used to evaluate the association of log₁₀-transformed biomarkers and potential confounders (e.g., plasma viral load, hormonal contraception, recent illness, body mass index) for

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clinical KS. Because the range of plasma ICAM-1 values spanned less than 1 log₁₀, and levels among cases had little overlap with levels among controls, this biomarker was dichotomized at above or equal to versus below the median (5.29 log₁₀ pg/mL).

All participants provided written informed consent. Ethical review committees of the Kenya Medical Research Institute, the University of Washington, and the Fred Hutchinson Cancer Research Center approved the study.

Characteristics of the 23 cases and 46 controls included in this study are shown in Table 1. The percentage of women receiving ART was the same in each group, and CD4 counts were similar. Median HIV-1 RNA, ANG-1, ANG-2, ICAM-1, and VEGF levels were higher in cases than controls, and median E-selectin and VCAM-1 levels were higher in controls than in cases. Levels of plasma viral load, ICAM-1, and ANG-2 for cases compared with controls are shown in Figure 1.

Results of conditional logistic regression comparing cases to matched controls are shown in Table 2. In bivariate analysis, the odds of KS was increased 2.5-fold with each log₁₀ copies/mL increase in HIV-1 RNA, and 10.3-fold for plasma ICAM-1 levels above or equal to the median. In addition, there was a borderline association ($P = 0.058$) between increasing plasma ANG-2 levels and KS, and each log₁₀ picogram/milliliter increase was associated with a 4.9-fold greater odds of clinical KS. In a multivariable model including plasma HIV-1 RNA, ANG-2, and ICAM-1, having plasma ICAM-1 above or equal to the median remained significantly associated with KS (odds ratio = 14.2, 95% confidence interval = 2.3–87.7). In a sensitivity analysis limiting the dataset to one randomly selected visit per control, results were unchanged.

In this case-control study, we aimed to identify plasma biomarkers associated with clinical KS in HIV-1-infected

women. We found that plasma viral load and ICAM-1 levels were significantly increased in cases relative to controls matched for visit year, ART status, and CD4 count. In addition, there was a borderline association between higher plasma ANG-2 levels, and clinical KS. In multivariable analysis, only ICAM-1 was significantly higher among cases relative to controls. We did not find differences between cases and controls with respect to E-selectin, VCAM-1, or VEGF.

Human herpes virus 8 or Kaposi sarcoma-associated herpes virus (KSHV) are known to infect lymphatic and vascular endothelial cells *in vitro*.¹³ Activation of NF-κB and other pathways by either KSHV or HIV-1 up-regulates expression of inflammatory cytokines and adhesion molecules, including ICAM-1, E-selectin, and VCAM-1.^{2,14–16} These adhesion molecules are associated with transmigration of lymphocytes into early KS lesions, further increasing inflammation.^{15,17} Ongoing immune activation is believed to stimulate endothelial cells to grow and acquire spindle cell morphology.²

KS cell cultures and spindle cells *in vivo* have been found to express ICAM-1 and, less consistently, VCAM-1.^{18–20} One small study published in 1997 reported that plasma ICAM-1 and VCAM-1 levels were increased in all patients with acquired immunodeficiency syndrome (AIDS),²¹ which is consistent with our study of HIV-1-seroconverters demonstrating increases in these two biomarkers after HIV-1 acquisition.⁴ However, Becker and others found that ICAM-1 levels were lower among KS patients than among AIDS controls,²¹ in contrast to our findings. In agreement with our findings, however, a 1994 study reported increased plasma ICAM-1 levels in HIV-1-infected patients with KS compared with healthy controls, HIV-infected patients with stage II or III disease, and HIV-infected patients with non-Hodgkin's lymphoma.²²

We also examined the relationship of plasma levels of ANG-2 with clinical KS. KSHV infection increases ANG-2

TABLE 1
Characteristics of 69 participants at reference visit, according to case or control status

Characteristic	All Participants (n = 69)	Cases (n = 23)	Controls (n = 46)
Age, years†	36 (34–40)	35 (33–38)	36.5 (34–42)
Education, years‡	7 (7–8)	7 (6–9)	7 (6.75–8.25)
Marital status‡			
Never married	21 (30.4)	3 (13.0)	18 (30.1)
Currently married	2 (2.9)	0	2 (4.3)
Widowed or divorced	46 (66.7)	20 (87.0)	26 (56.5)
Live births‡	2 (1–3)	2 (1–3)	3 (1–4)
Workplace‡			
Bar or guesthouse	50 (72.5)	13 (56.5)	37 (80.4)
Night club	8 (11.6)	3 (13.0)	5 (10.9)
Other	11 (15.9)	7 (30.4)	4 (8.7)
Hormonal contraceptive use†	17 (24.6)	6 (26.0)	11 (23.9)
Body mass index, kg/m ² †	25.4 (22.8–30.5)	26.4 (24.3–31.3)	24.4 (21.1–30.3)
Too sick to work†	5 (7.2)	3 (13.0)	2 (4.3)
Taking ART†	15 (21.7)	5 (21.7)	10 (21.7)
CD4 count, cells/μL†	212 (90–299)	196 (70–313)	217.5 (89.5–321)
HIV-1 RNA, log ₁₀ copies/mL†	4.89 (3.98–5.81)	5.44 (4.69–6.02)	4.47 (3.70–5.73)
Angiopoietin 1, log ₁₀ pg/mL†	4.16 (4.03–4.25)	4.21 (4.10–4.25)	4.13 (3.99–4.23)
Angiopoietin 2, log ₁₀ pg/mL†	2.58 (2.39–2.81)	2.68 (2.41–3.10)	2.54 (2.35–2.78)
ICAM-1, log ₁₀ pg/mL†	5.29 (5.23–5.33)	5.33 (5.30–5.36)	5.25 (5.20–5.31)
E-selectin, log ₁₀ pg/mL†	4.46 (4.29–4.55)	4.42 (4.28–4.54)	4.48 (4.29–4.57)
VCAM-1, log ₁₀ pg/mL†	5.88 (5.82–6.00)	5.88 (5.82–6.10)	5.89 (5.81–5.99)
VEGF, log ₁₀ pg/mL†	1.78 (1.43–2.04)	1.80 (1.52–2.11)	1.78 (1.41–1.99)

Values indicate no. (%) of participants or median (interquartile range). Case patients were defined as HIV-1-infected women with a clinical diagnosis of Kaposi's sarcoma. For each case patient, two control participants, defined as HIV-1-infected women without Kaposi's sarcoma, were selected and matched to case patients for antiretroviral therapy status, CD4 count (within 100 cells/μL), and calendar year of visit. Some data were missing for live births (n = 1) and body mass index (n = 5). ART = antiretroviral therapy; HIV-1 = human immunodeficiency virus 1; ICAM-1 = intracellular adhesion molecule 1; VCAM-1 = vascular cell adhesion molecule 1; VEGF = vascular endothelial growth factor.

† Collected at the included visit.

‡ Collected at cohort enrollment.

FIGURE 1. Log₁₀-transformed plasma human immunodeficiency virus 1 (HIV-1) RNA (A), intercellular adhesion molecule 1 (ICAM-1) (B), and Angiopoietin 2 (ang-2) (C) comparing cases with controls. Solid circles represent individual data points. Horizontal lines through the data points represent group median values.

transcription in endothelial cells,^{3,13,23} and induces release of preformed ANG-2 from Weibel-Palade bodies.²⁴ One previous study reported that plasma ANG-2 and VEGF-D levels were increased in persons with KS compared with healthy and HIV-infected controls.¹³ Interestingly, plasma levels of ANG-2 and VEGF-D were significantly lower during resolution of KS among patients taking ART.¹³

TABLE 2

Conditional logistic regression with odds ratio comparing cases with controls*

Characteristic	Odds ratio (95% CI)	P	Adjusted odds ratio (95% CI)	P
Age, years	0.96 (0.88–1.05)	0.42		
Hormonal contraceptive use	1.12 (0.36–3.51)	0.84		
Body mass index, kg/m ²	1.03 (0.94–1.13)	0.53		
Too sick to work	4.65 (0.47–46.23)	0.19		
HIV-1 RNA, log ₁₀ copies/mL	2.48 (1.19–5.17)	0.016	2.23 (0.75–6.64)	0.15
Angiopoietin 1, log ₁₀ pg/mL	3.92 (0.21–72.81)	0.36		
Angiopoietin 2, log ₁₀ pg/mL	4.86 (0.95–24.91)	0.058	12.81 (0.54–305.67)	0.12
Log ₁₀ ratio of ANG-2 to ANG-1	2.76 (0.61–12.51)	0.19		
ICAM-1 ≥ median (5.29 log ₁₀ pg/mL)	10.28 (2.32–45.61)	0.002	14.16 (2.28–87.74)	0.004
E-selectin, log ₁₀ pg/mL	0.94 (0.04–21.92)	0.97		
VCAM-1, log ₁₀ pg/mL	5.37 (0.45–64.75)	0.19		
VEGF, log ₁₀ pg/mL	1.36 (0.60–3.09)	0.46		

*CI = confidence interval; HIV-1 = human immunodeficiency virus 1; ANG-2 = angiopoietin 2; ANG-1 = angiopoietin 1; ICAM-1 = intracellular adhesion molecule 1; VCAM-1 = vascular cell adhesion molecule 1; VEGF = vascular endothelial growth factor.

Although ANG-2 levels were somewhat higher among KS cases than controls in our study, this finding was only of borderline significance. The Angiopoietin/Tie-2 system has been identified as a potential target for therapeutic drug development in KS,²⁵ and further study of this molecule and its potential role as a biomarker at different stages of KS disease progression is warranted.

Our study had several limitations. First, we relied on clinical diagnosis of KS because biopsy and pathology services were not available when women were seen. It will be important to confirm our findings using biopsy-proven KS cases. Second, the number of cases was small, limiting power to detect differences. Third, this study included only women attending a clinic for female sex workers; cases and controls were selected from the same population. Therefore, it is unclear that results are generalizable to other women or men in Africa. Finally, we were unable to test all candidate biomarkers of angiogenesis (e.g., VEGF-D) because of limited sample quantity. However, strengths of the study include the standardized approach to physical examination, with lesions compatible with KS recorded at every visit; storage of blood samples from HIV-infected women with and without KS at multiple visits; randomized selection of controls matched to cases; and meticulous testing for biomarkers in an experienced laboratory.

In conclusion, we have found that plasma ICAM-1 levels are higher among women with clinical KS, compared with HIV-infected controls matched for calendar year, CD4 count, and ART status. ANG-2 levels, although higher in cases, were not significantly associated with clinical KS. Further research is needed to evaluate the role of adhesion molecules and pro-angiogenic molecules in KS pathogenesis and disease progression. Plasma ICAM-1 levels, in particular,

may have utility as a biomarker of disease progression and treatment response.

Received April 7, 2014. Accepted for publication June 3, 2014.

Published online July 7, 2014.

Acknowledgments: We thank the research staff for their contributions, the Mombasa Municipal Council for clinical space, the Coast Provincial General Hospital for laboratory space, Vrasa Chohan for coordination of laboratory sample shipments, and the study participants for their cooperation.

Financial support: This study was supported by a New Investigator Award to Susan M. Graham from the University of Washington Center for AIDS Research, which is supported by the National Institutes of Health (NIH) (grant no. P30 AI027757); the National Institute of Allergy and Infectious Diseases, the National Cancer Institute, the National Institute of Mental Health, the National Institute on Drug Abuse, the National Institute of Child Health and Human Development, the National Heart, Lung, and Blood Institute, and the National Institute on Aging (grants AI-58698 and AI-38518); and by a Canada Research Chair in Infectious Diseases and Inflammation to W. Conrad Liles from the Canadian Institutes for Health Research.

Disclosure: W. Conrad Liles is listed as a co-inventor on a patent applied for by the University Health Network (Toronto, ON, Canada) to develop point-of-care tests for endothelial activation biomarkers in infectious diseases. All other authors report no conflicts of interest.

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