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Short Report: Intestinal Parasites in Kaposi Sarcoma Patients in Uganda: Indication of Shared Risk Factors or Etiologic Association

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Abstract. Kaposi sarcoma (KS) is endemic in Uganda and shares several risk factors with intestinal parasite infestation, including rural residence, contact with surface water, and walking barefoot, however, the significance of these ecologic relationships is unknown. We investigated these relationships among 1,985 Ugandan patients with cancer. Odds ratios (OR) were calculated using logistic regression. KS patients had higher carriage of *Strongyloides stercoralis* larvae (OR 2.1, 95% CI 1.2–3.7) and lower carriage of hookworm ova (0.6, 0.4–1.0) and *Entamoeba coli* cysts (0.7, 0.5–1.0), after adjusting for region of residence, age, gender, and diagnosis. While our findings may be due to confounding, they are compatible with shared risk factors or etiological association between parasites and KS, and warrant well-designed follow up studies.

Kaposi sarcoma (KS) is endemic in equatorial Africa, but its incidence has increased substantially with the advent of the AIDS epidemic,[1] calling attention to immunosuppression as a co-factor. Human herpesvirus 8 (HHV8, also known as KS-associated herpesvirus or KSHV), is necessary for KS to develop.[2] However, HHV8 pathogenicity is low in immunocompetent persons,[3] suggesting contribution from co-factors. In Uganda, before the onset of AIDS, endemic KS was unevenly distributed, accounting for ~5% of cancers diagnosed in the central districts and 18% of cancers diagnosed in the West Nile districts.[4] Correspondingly, adult non–HIV-related HHV8 seroprevalence seems lower in the central districts than in other districts,[5,6] including the West Nile districts,[7] but the differences do not sufficiently account for the geographic variation in endemic KS.[5]

Risk factors for KS include rural residence, walking barefoot, peasant farming, contact with surface water, and male sex.[8] These risk factors point to environmental or outdoor exposure as playing an important role in KS risk. However, they are also risk factors for infection with intestinal parasites.[9] Interestingly, co-occurrence of KS in patients with helminthic parasites has been noted,[10] but whether KS patients are more likely to be infected with intestinal parasites has not been assessed in analytic studies. To test this hypothesis, we examined the frequencies of intestinal parasite carriage among KS patients and other cancer patients in Uganda.

We studied 943 KS patients and 1,042 other cancer patients admitted to the Uganda Cancer Institute (UCI) between 1994 and 2004. The UCI provides medical oncology services to histologically confirmed cancer patients. Before treatment, all patients are screened by stool microscopy to determine presence of abnormal cells and specific intestinal parasites. We abstracted basic demographic information, including admission date, age, sex, tribe, region of residence, cancer diagnosis, and stool microscopy results from laboratory accession books. We examined associations between KS and selected patient characteristics with odds ratios (ORs) and 95% confidence intervals (CIs) from logistic regression models. We examined the independent association of variables with KS using multivariable logistic regression models by simultaneously including all variables. Two-sided $P < 0.05$ was considered statistically significant.

Table 1 shows selected patient characteristics. The most frequent cancers other than KS included 261 (25%) non-Hodgkin lymphomas (NHL), 246 (24%) breast cancers, 106 (10%) leukemias, 77 (7%) other sarcomas, and 69 (7%) Hodgkin lymphomas. Compared with other cancer patients, KS patients were more frequently men and significantly younger. Residences of KS patients were overrepresented in the central districts and underrepresented in the northern districts. KS patients had been admitted from 1994 to 1999, whereas other cancer patients had been admitted from 1994 to 2004.

Overall, KS patients had diarrheal stools noted more frequently compared with other cancer patients (14% versus 6.1%; OR, 2.6; 95% CI, 1.9–3.5). Furthermore, mucoid material and/or abnormal cells (red blood cells, pus, and yeasts) were present more frequently in stools of KS patients than in stools of other cancer patients (5.4% versus 1.5%; OR, 3.7; 95% CI, 2.1–6.5). We found no differences between the proportion of KS patients and of other cancer patients with all intestinal parasites combined (25% versus 28%; OR, 0.9; 95% CI, 0.7–1.1). However, we did find significant differences between KS patients and other cancer patients in the frequency of specific parasite types (Figure 1). Compared with other cancer patients, KS patients were more likely to carry *Strongyloides stercoralis* larvae (6.0% versus 3.1%; OR, 2.0; 95% CI, 1.3–3.2). Furthermore, ova or cysts of *Schistosoma mansoni*, *Giardia lamblia*, *Trichomonas hominis*, and *Entamoeba histolytica* were detected more frequently in KS patients, but the differences were not statistically significant. In contrast, hookworm ova and *Entamoeba coli* ova or cysts were detected less frequently in KS patients than in other cancer patients (OR, 0.7; 95% CI, 0.6–1.0 and OR, 0.8; 95% CI, 0.6–1.1, respectively). In analyses simultaneously adjusting for all covariates (sex, age, admission year, region of residence, and presence of *S. stercoralis*, hookworm, and *E. coli*), KS was positively associated with male sex (OR, 3.0; 95% CI, 2.4–3.9), age < 35 years (OR, 3.6; 95% CI, 2.8–4.6), and carrying *S. stercoralis* (OR, 2.1; 95% CI, 1.2–3.7) and inversely associated with hookworm (OR, 0.6; 95% CI, 0.4–1.0) and *E. coli* (OR, 0.7; 95% CI, 0.5–1.0).

We found that about one quarter of patients at the UCI had

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TABLE 1
Demographic characteristics of patients with KS and control cancers

Characteristic		KS	Other cancer	*P*
Sex	Female	311 (33.0%)	592 (56.8%)	< 0.001
	Male	632 (67.0%)	450 (43.2%)	
Age group (years)	< 25	94 (10.0%)	107 (10.3%)	< 0.001*
	25–34	445 (47.2%)	191 (18.3%)	
	35–44	239 (25.3%)	270 (25.9%)	
	45–54	99 (11%)	206 (19.8%)	
	55+	66 (7.0%)	268 (25.7%)	
Residence district	Central	675 (71.6%)	695 (66.7%)	0.02
	Western	106 (11.2%)	111 (10.7%)	
	Northern	35 (3.7%)	60 (5.8%)	
	Eastern	127 (13.5%)	176 (16.9%)	
Admission year	1994–1996	416 (44.1%)	83 (8.0%)	< 0.001
	1997–1999	527 (55.9%)	493 (47.3%)	
	2000–2002	0 (0%)	371 (35.6%)	
	2003–2004	0 (0%)	95 (9.1%)	

* Age fitted as a trend across category.

stool parasites. This result is similar to findings in a previous study from the same institute[11] but substantially lower than (about one half) the prevalence reported in studies characterizing stool parasite infection elsewhere in Uganda.[12] Compared with studies conducted in other developing countries, our prevalence estimate is lower than in Ethiopia, where up to 70% of adults had intestinal parasites,[13] but it is similar to results from Zambia[14] and Tanzania,[15] where ~25% and 35%, respectively, of HIV-infected adults had parasites detected in their stool. However, comparing parasite prevalence in different studies is risky because variability is influenced by multiple factors, including method of stool examination, sample size, and behavioral and ecologic patterns that influence the prevalence, intensity, and the specific parasites involved. In our study, the overall prevalence of intestinal parasites among patients with KS and other cancers was similar. However, we found significant differences in the carriage of specific parasites, suggesting that infection status with specific parasite types may modulate, through immunologic mechanisms, KS risk.

KS patients had a higher prevalence of *S. stercoralis* carriage than patients with other cancers. This observation echoes a previous report that noted co-occurrence of onchocerciasis with KS.[10] The correlation between KS and luminal or tissue parasites may be caused by common risk factors for parasites and KS, or it may indicate an etiologic association. For example, *S. stercoralis* is capable of multiplying even in the immunocompetent host, and filariform larvae in the upper small bowel can re-invade through the colonic mucosa or the peri-anal areas, creating a long lasting infection and immunologic modulation. After infection, intestinal parasites downregulate T helper (Th)-1 cellular responses and upregulate Th-2 humoral responses.[16] These immunologic changes may render the infected host unable to effectively control viral infection. Plausibly, infection with *S. stercoralis* may be associated with poor control of lytically replicating HHV8, expansion of HHV8-infected B cells in the peripheral blood, and a heightened risk for KS. Although biologically plausible, reports of disseminated strongyloidiasis as a feature of KS distinctively rare.[17,18]

Confounding by HIV infection, which is a risk factor for KS[19] and may increase the risk for *S. stercoralis,*[20] is possible. To address this question, we performed a sensitivity analysis to assess to what extent HIV may explain our findings. Because we lacked individual data on HIV status, we used published data on HIV prevalence among cancer patients treated at the UCI during the 1990s.[19,21] The impact of HIV infection on carriage of *S. stercoralis* is not well understood.[18] In Uganda, *S. stercoralis* larvae are detected frequently in HIV-infected patients[22]; however, disseminated strongyloidiasis is rare, and the risk of carriage of *S. stercoralis* among HIV-infected versus uninfected is unknown. Among HIV-infected persons, lower CD4 lymphocyte counts was associated with indirect, rather than direct, development of *S. stercoralis*.[23] Because direct development is needed for hyperinfection associated with disseminated strongyloidiasis, these results suggest an explanation for the infrequency of disseminated strongyloidiasis in persons with HIV infection in countries such as Uganda despite relatively common carriage. Thus, for our sensitivity analyses, we assumed that HIV-infected per-

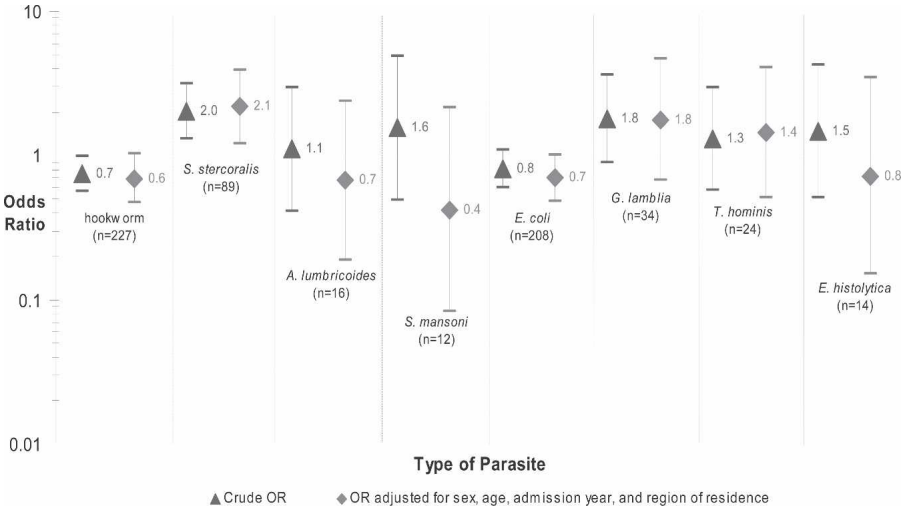

FIGURE 1. Graph shows crude and adjusted associations of KS with specific types of intestinal parasites detected in stool of patients at the UCI. Numbers in parentheses are total number of KS and other cancer patients. Midpoints mark the OR, and the bars at the end of the lines mark the lower and upper 95% CI for the OR.

sons are 2-fold more likely to carry *S. stercoralis* larvae compared with uninfected persons; therefore, the postulated effect size was similar to that observed between *S. stercoralis* and KS. Thus, assuming that 71% of KS patients,[19] 62% of NHL patients, and 21% of other cancer patients[21] were HIV-infected and that HIV infection doubles the risk for *S. stercoralis* detection, one would expect a 1.3-fold association of KS with *S. stercoralis*. Based on these assumptions, we estimate that ~60% of the observed association could be explained by confounding with HIV infection.

Our findings of inverse associations between KS and hookworm or *E. coli* were unexpected. Because the probability of infection with specific parasite species may vary by geography, we performed analyses stratified by region and tribe and obtained essentially similar results. Possibly, patients with KS may be more likely to receive anti-helminthic drugs than other cancer patients. This difference could be caused by Ugandan physicians considering the risk factors for intestinal or tissue parasite infestation, i.e., rural residence, contact with surface water, and walking barefoot, which coincidentally are risk factors for KS,[8] and therefore prescribing anti-helminthics to KS patients. HIV infection may confound the associations because immunosuppression has been reported to decrease egg production by hookworms, which could result in lower frequency of detection in stool.[24] Alternatively, epidemic KS is associated with higher socioeconomic indicators, possibly lowering exposure to ova-contaminated soils.[25]

The strengths of our pilot study include its relatively large size, detailed data on specific stool parasites measured on admission, the novelty of the associations examined, and the hypotheses it explores. Nonetheless, several limitations remain. First, the study is cross-sectional; thus, the temporality of the associations cannot be determined. Our results are based on examining only one stool sample, which has less optimal sensitivity and would attenuate our findings, especially for species that are hard to detect like *S. stercoralis*. Second, we did not have HIV status for the patients to more precisely ascertain the degree of confounding. Third, referral bias to the UCI limits generalizability of our findings. Finally, we lacked information on prior anti-helminthic treatment and other exposure data, which might explain the inverse associations with hookworm. Nonetheless, our results provide additional reasons to study relationships between KS and infection with intestinal parasites.

To summarize, the novel associations are positive association of KS with carriage of *S. stercoralis* larvae and inverse associations with hookworm ova and *E. coli* cysts. The significance of these associations is uncertain, but they raise questions about a possible etiologic relationship between KS and intestinal parasites that should be addressed in studies using a prospective design, controlling for HIV, socioeconomic indicators, and other confounders.

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REFERENCES

1. Wabinga HR, Parkin DM, Wabwire-Mangen F, Nambooze S, 2000. Trends in cancer incidence in Kyadondo County, Uganda, 1960–1997. *Br J Cancer 82:* 1585–1592.
2. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, Moore PS, 1994. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science 266:* 1865–1869.
3. Vitale F, Briffa DV, Whitby D, Maida I, Grochowska A, Levin A, Romano N, Goedert JJ, 2001. Kaposi's sarcoma herpes virus and Kaposi's sarcoma in the elderly populations of 3 Mediterranean islands. *Int J Cancer 91:* 588–591.
4. Templeton AC, Hutt MS, 1973. Distribution of tumours in Uganda. *Recent Results Cancer Res 41:* 1–22.
5. Mbulaiteye SM, Biggar RJ, Pfeiffer RM, Bakaki PM, Gamache C, Owor AM, Katongole-Mbidde E, Ndugwa CM, Goedert JJ, Whitby D, Engels EA, 2005. Water, socioeconomic factors, and human herpesvirus 8 infection in Ugandan children and their mothers. *J Acquir Immune Defic Syndr 38:* 474–479.
6. Newton R, Ziegler J, Bourboulia D, Casabonne D, Beral V, Mbidde E, Carpenter L, Reeves G, Parkin DM, Wabinga H, Mbulaiteye S, Jaffe H, Weiss R, Boshoff C, 2003. The sero-epidemiology of Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) in adults with cancer in Uganda. *Int J Cancer 103:* 226–232.
7. de-The G, Bestetti G, van Beveren M, Gessain A, 1999. Prevalence of human herpesvirus 8 infection before the acquired immunodeficiency disease syndrome-related epidemic of Kaposi's sarcoma in East Africa. *J Natl Cancer Inst 91:* 1888–1889.
8. Ziegler J, Newton R, Bourboulia D, Casabonne D, Beral V, Mbidde E, Carpenter L, Reeves G, Parkin DM, Wabinga H, Mbulaiteye S, Jaffe H, Weiss R, Boshoff C, 2003. Risk factors for Kaposi's sarcoma: a case-control study of HIV-seronegative people in Uganda. *Int J Cancer 103:* 233–240.
9. Handzel T, Karanja DM, Addiss DG, Hightower AW, Rosen DH, Colley DG, Andove J, Slutsker L, Secor WE, 2003. Geographic distribution of schistosomiasis and soil-transmitted helminths in Western Kenya: implications for anthelminthic mass treatment. *Am J Trop Med Hyg 69:* 318–323.
10. Williams EH, Williams PH, 1966. A note on an apparent similarity in distribution of onchocerciasis, femoral hernia and Kaposi's sarcoma in the West Nile district of Uganda. *East Afr Med J 43:* 208–209.
11. Robinson AJ, Katongole-Mbidde E, 2006. Gastrointestinal parasites in Ugandan cancer patients: a retrospective departmental review. *Trop Doct 36:* 188–189.
12. Brown M, Miiro G, Nkurunziza P, Watera C, Quigley MA, Dunne DW, Whitworth JA, Elliott AM, 2006. Schistosoma mansoni, nematode infections, and progression to active tuberculosis among HIV-1-infected Ugandans. *Am J Trop Med Hyg 74:* 819–825.
13. Fontanet AL, Sahlu T, Rinke de Wit T, Messele T, Masho W, Woldemichael T, Yeneneh H, Coutinho RA, 2000. Epidemiology of infections with intestinal parasites and human immunodeficiency virus (HIV) among sugar-estate residents in Ethiopia. *Ann Trop Med Parasitol 94:* 269–278.
14. Kelly P, Baboo KS, Wolff M, Ngwenya B, Luo N, Farthing MJ, 1996. The prevalence and aetiology of persistent diarrhoea in adults in urban Zambia. *Acta Trop 61:* 183–190.
15. Tarimo DS, Killewo JZ, Minjas JN, Msamanga GI, 1996. Prevalence of intestinal parasites in adult patients with enteropathic AIDS in north-eastern Tanzania. *East Afr Med J 73:* 397–399.
16. Kamal SM, El Sayed Khalifa K, 2006. Immune modulation by helminthic infections: worms and viral infections. *Parasite Immunol 28:* 483–496.
17. Murphy RA, Barton G, Pinkas H, Schaefer R, 1991. Severe colitis due to Strongyloides stercoralis in a patient with cutaneous Kaposi's sarcoma. *Gastrointest Endosc 37:* 79–82.
18. Lucas SB, 1990. Missing infections in AIDS. *Trans R Soc Trop Med Hyg 84 (Suppl 1):* 34–38.

19. Newton R, Ziegler J, Bourboulia D, Casabonne D, Beral V, Mbidde E, Carpenter L, Parkin DM, Wabinga H, Mbulaiteye S, Jaffe H, Weiss R, Boshoff C, 2003. Infection with Kaposi's sarcoma-associated herpesvirus (KSHV) and human immunodeficiency virus (HIV) in relation to the risk and clinical presentation of Kaposi's sarcoma in Uganda. *Br J Cancer 89:* 502–504.
20. Brown M, Mawa PA, Kaleebu P, Elliott AM, 2006. Helminths and HIV infection: epidemiological observations on immunological hypotheses. *Parasite Immunol 28:* 613–623.
21. Newton R, Ziegler J, Beral V, Mbidde E, Carpenter L, Wabinga H, Mbulaiteye S, Appleby P, Reeves G, Jaffe H, 2001. A case-control study of human immunodeficiency virus infection and cancer in adults and children residing in Kampala, Uganda. *Int J Cancer 92:* 622–627.
22. Brink AK, Mahe C, Watera C, Lugada E, Gilks C, Whitworth J, French N, 2002. Diarrhea, CD4 counts and enteric infections in a community-based cohort of HIV-infected adults in Uganda. *J Infect 45:* 99–106.
23. Viney ME, Brown M, Omoding NE, Bailey JW, Gardner MP, Roberts E, Morgan D, Elliott AM, Whitworth JA, 2004. Why does HIV infection not lead to disseminated strongyloidiasis? *J Infect Dis 190:* 2175–2180.
24. Viney M, 2002. How do host immune responses affect nematode infections? *Trends Parasitol 18:* 63–66.
25. Ziegler JL, Newton R, Katongole-Mbidde E, Mbulataiye S, De Cock K, Wabinga H, Mugerwa J, Katabira E, Jaffe H, Parkin DM, Reeves G, Weiss R, Beral V, 1997. Risk factors for Kaposi's sarcoma in HIV-positive subjects in Uganda. *AIDS 11:* 1619–1626.