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ABSTRACT

Objective: Kaposi's sarcoma-associated herpesvirus (KSHV) is the causative agent for Kaposi's sarcoma (KS), one of the most common cancers in Tanzania. We have investigated KSHV prevalence and factors associated with KSHV infection in Tanzania.
Methods: This is a cross-sectional study of voluntary blood-donors from Dar es Salaam, Tanzania. Plasma was screened for KSHV, HIV-1, HBV, HCV and *Treponema pallidum* (syphilis). Associations between KSHV sero-status and risk factors were analyzed. Odds ratios (OR) and 95% confidence intervals (CI) are reported to evaluate risk factors of KSHV infection. All tests were 2-tailed, and *P*-values <0.05 were considered statistically significant.
Results: The overall KSHV seroprevalence was 56.9%. Significantly increased risk of KSHV infection was detected in persons from the Lake and Central Zones (OR = 6.4, 95% CI = 1.6–25.3, *P* = 0.008 and OR = 5.7, 95% CI = 1.0–32.5, *P* = 0.048 respectively). A trend toward increased risk of KSHV infection with HIV-1 co-infection was not significant (OR = 2.8, 95% CI = 1.0–8.0, *P* = 0.06). Seroreactivity to *T. pallidum* was surprisingly high (14.9%).
Conclusion: The prevalence of KSHV infection and syphilis was high among Tanzanian blood-donors. The most common transfusion-transmissible infections did not associate with KSHV infection. Regions of focal KSHV infection need further investigation for underappreciated risk factors.

1. Introduction

Kaposi's sarcoma-associated herpesvirus (KSHV) is etiologically linked with Kaposi's sarcoma (KS), primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD) (Chang et al., 1994; Cesarman et al., 1995; Moore and Chang, 1995; Soulier et al., 1995). The virus is unequally distributed geographically with KSHV infection endemic in sub-Saharan Africa (SSA), some parts of Eastern Europe and Mediterranean and some ethnicities in China (Dedicoat and Newton, 2003; de Sanjose et al., 2009; Dollard et al., 2010; Zheng et al., 2017). Consequently, the burden of KS is highest in SSA where two distinct forms, African endemic KS (EnKS), and HIV-1-associated/Epidemic KS (EpKS) are common. Levels of EnKS continue relatively unchanged from pre-HIV-1 epidemic levels of 4 to 10% of all sub-Saharan cancers (Cook-Mozaffari et al., 1998); whereas, EpKS is now the most common cancer in people living with HIV-1 infection in SSA (Bohlius et al., 2014; Rohner et al., 2014; Ngalamika et al., 2015; Semeere et al., 2016). While KSHV prevalence is high in Uganda and Zambia, two neighboring countries to Tanzania, the prevalence of this infection is not clear in Tanzania (Minhas and Wood, 2014; Newton et al., 2018b).

Infection with KSHV is life-long, and most infections detected in African adults occurred during childhood (Mbulaiteye et al., 2003; Minhas et al., 2008a; Butler et al., 2009b; Cao et al., 2014b; Nalwoga et al., 2018). The majority of KSHV infection occurs in childhood resulting in about 50% seroprevalence in sub-Saharan children before their fourth birthday (Minhas et al., 2008a). Saliva has been implicated as the major vehicle of KSHV transmission from which children get infected within and outside of households

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(Crabtree et al., 2014). Practices like premastication of baby food, application of saliva to wounds or using a saliva-soaked finger on anorectal regions of constipated children have all been suggested to increase the risk of KSHV infection in SSA (Butler et al., 2009a; Crabtree et al., 2014). While HIV-1 infection has been identified as a risk factors for KSHV infection in children, recent studies in adult Ugandans and Cameroonians did not recapitulate these findings (Minhas et al., 2008a; Butler et al., 2009a; Newton et al., 2018a; Labo et al., 2019).

In a recent study from northern Tanzania, transfusion-transmissible infections (TTI) contributed to 62% of all blood donor rejection and destruction of collected blood donor samples. Infections with hepatitis B and C, HIV-1 and syphilis were the common causes of rejection and destruction of collected blood donor samples (Valerian et al., 2018). Unfortunately, the prevalence of KSHV was not investigated, as KSHV is not routinely screened prior to transfusions in Tanzania. Importantly, the KSHV prevalence in the Tanzanian general population is not clear as varying prevalence have been reported (Enbom et al., 2002; Mbulaiteye et al., 2003). In this study, we recruited voluntary non-remunerated blood donors to investigate the prevalence of common infectious organisms and their association with KSHV infection in order to fill the existing knowledge gap and ultimately define strategies to reduce the infection.

2. Materials and methods

2.1. Study design, subjects and samples

This cross-sectional study utilized blood samples from 504 consecutively recruited, voluntary non-remunerated blood donors in Dar es Salaam, Tanzania from February to May 2019. The blood donation centers were located in all 5 districts of Dar es Salaam region. The blood donors were of both genders and over 18 years of age according to the national blood donation guidelines (United Republic of Tanzania, 2015). Blood samples were collected in EDTA vacutainers and plasma was isolated by centrifugation. Written informed consent was obtained from all study participants. The study was approved by the review boards of Tanzania National Institute for Medical Research, Ocean Road Cancer Institute and the University of Nebraska-Lincoln (UNL).

2.2. KSHV screening by immunofluorescence assay (IFA)

To determine KSHV serological status, an immunofluorescence assay (IFA) was performed on plasma samples as previously described (Minhas et al., 2008b). To reduce subjectivity in status assignations, slides were independently read by two readers.

2.3. HIV-1, HBsAg, HCV and syphilis screening

The Tanzania National Blood Transfusion Service (NBTS) transfusion-transmissible infections (TTIs) algorithm was used to screen for TTIs by enzyme-linked immunosorbent assay (ELISA), except as indicated. The Murex HIV Ag/Ab ELISAtest was used to screen for HIV-1. A Murex HBsAg version 3.0 ELISA test was used for HBsAg and Murex HCV Ag/Ab combination ELISA test for HCV (DiaSorin, Saluggia, Italy) as previously described (Valerian et al., 2018). The Espline *Treponema pallidum* rapid test (Mast group, Merseyside, UK) was used to screen for syphilis as previously described (Valerian et al., 2018).

2.4. Statistical analysis

Descriptive statistics were generated by frequency tables. Associations between KSHV sero-status and risk factors were analyzed by using the Pearson Chi-square test of independence. Estimation of effect size (prevalence odds ratios), as well as the direction and magnitude of effect, were performed using binary, logistic regression modeling of risk factors of KSHV infection. All study variables were included in the adjusted regression model. Prevalence Odds Ratio (POR) and 95% confidence intervals (CI) were reported to evaluate the risk factors of KSHV infection. All tests were 2-tailed, and P-value <0.05 was considered statistically significant. Data visualization, exploration and all analysis were performed with SAS version 9.4 software (SAS Institute, Cary, NC).

3. Results

3.1. Characteristics of the study cohort

To investigate the prevalence of common infectious organisms and their association with KSHV infection in Tanzanian blood donors, we tested a total of 504 adults from Dar es Salaam, Tanzania. The median age of the cohort was 31 years and ranged between 18 and 58 years. Consistent with previous studies in Tanzania, the majority of blood donors in Tanzania were male (85.5%) and married (59.7%) (Elias et al., 2016; Mohammed and Essel, 2018; Valerian et al., 2018). The main occupational activities reported by blood donors were small business vendors (71.8%), followed by being a student (Table 1). While the majority of the participants (48%) were born in the coastal zone, comprised of Dar es Salaam, Morogoro and Pwani, the entire country was represented when considering participants' places of birth (Fig. 1). Place of birth is particularly relevant because most infections with KSHV occur during early childhood and therefore the observed KSHV prevalence could be used as a surrogate prevalence for participants' places of birth (Minhas et al., 2008a; Cao et al., 2014a; Crabtree et al., 2014).

3.2. Prevalence of KSHV infection in Tanzanian blood donors

KSHV infection in Tanzania has always been suspected to be high but has not been reported from a cohort of sufficient size to provide population estimates of seroprevalence. An immunofluorescence assay (IFA) that detects antibodies against both latent and lytic KSHV antigens expressed by mitogen-stimulated KSHV-infected BC3 cells was utilized to determine KSHV seroprevalence. Overall, 56.9% of the participants were KSHV positive (Fig. 1). Anti-KSHV antibody detection by IFA was not associated with the age, gender, marital status or occupation of the blood donors.

3.3. Prevalence of transfusion-transmissible infections in Tanzanian blood donors

Unmet needs for blood for transfusion are a cause of significant morbidity and mortality. In Tanzania, less than a third of the actual needs of blood is collected. A recent study showed that about 12% of the voluntary blood donors are deferred from blood donations. TTI are the main cause for deferrals. We investigated the common TTIs among Tanzanian blood donors. The prevalence of HIV-1 infection in the cohort was 4.2%, close to the national average of 4.9% (TACAIDS et al., 2018). HBV and HCV infections were at 7.3% and 3.2% respectively. Disturbingly, anti-syphilis antibodies were common among blood donors at a higher than anticipated frequency (14.9%) (Table 1).

3.4. Association between KSHV and other risk factors

To determine factors association with risk of KSHV infection, we analyzed the relationship between KSHV infection and other measured variables in the cohort. Overall, infections with more

Table 1
Univariate and multivariate logistic regression analysis of risk factors of KSHV infection in Tanzania

Variables		Univariate			Multivariate		
		Odds ratio	*P*-value	95% CI	Odds ratio	*P*-value	95% CI
Age	*N* = 504						
Median (range)	31 (18-58)	1.00	0.900	0.9–1.02	1.00	0.895	0.98–1.03
Gender	*N* = 504						
Female (%)	73 (14.5)	–	–	–	–	–	–
Male (%)	431 (85.5)	1.3	0.200	0.8–2.2	1.4	0.210	0.8–2.4
Marital status	*N* = 504						
Single (%)	199 (39.5)	–	–	–	–	–	–
Married (%)	301 (59.7)	0.9	0.584	0.6–1.3	0.8	0.435	0.5–1.4
Divorced (%)	4 (0.8)	2.1	0.512	0.2–20.9	2.4	0.456	0.2–24.7
Place of birth	*N* = 504						
Zanzibar (%)	14 (2.8)	–	–	–	–	–	–
Central (%)	12 (2.4)	5.4	0.052	1.0–29.7	5.7	**0.048**	1.0–32.5
Coastal (%)	242 (48.0)	2.2	0.160	0.7–6.9	2.4	0.144	0.7–7.6
Lake zone (%)	35 (6.9)	4.5	**0.025**	1.2–16.8	6.4	**0.008**	1.6–25.3
Northern (%)	56 (11.1)	2.8	0.100	0.8–9.4	3.0	0.090	0.8–10.5
Southern (%)	82 (16.3)	1.9	0.289	0.6–6.1	2.0	0.264	0.6–6.8
Southern highlands (%)	30 (6.0)	2.4	0.200	0.6–8.7	2.6	0.163	0.7–10.4
Western	33 (6.5)	3.2	0.084	0.9–11.6	3.4	0.075	0.9–12.9
Occupation	*N* = 504						
Farmers (%)	27 (5.4)	–	–	–	–	–	–
Fishermen (%)	2 (0.4)	–	0.987	–		0.987	
Health workers (%)	8 (1.6)	1.1	0.870	0.2–5.8	1.2	0.804	0.2–6.7
Public servants (%)	46 (9.1)	0.8	0.347	0.3–1.9	0.6	0.373	0.2–1.7
Students (%)	59 (11.7)	1.0	0.562	0.4–2.2	0.6	0.352	0.2–1.7
Small business (%)	362 (71.8)	0.6	0.966	0.2–1.6	1.1	0.848	0.5–2.5
HIV-1 status	*N* = 504						
Negative (%)	483 (95.8)	–	–	–	–	–	–
Positive (%)	21 (4.2)	2.5	0.080	0.9–6.9	2.8	0.055	1.0–8.0
HBsAg status	*N* = 504						
Negative (%)	467 (92.7)	–	–	–	–	–	–
Positive (%)	37 (7.3)	1.4	0.300	0.7–2.9	1.3	0.479	0.6–2.7
HCV status	*N* = 504						
Negative (%)	488 (96.8)	–	–	–	–	–	–
Positive (%)	16 (3.2)	1.7	0.300	0.6–4.9	1.8	0.333	0.6–5.6
Syphilis status	*N* = 504						
Negative (%)	429 (85.1)	–	–	–	–	–	–
Positive (%)	75 (14.9)	1.0	0.900	0.6–1.6	1.0	0.987	0.6–1.7

HBsAg – Hepatitis B surface antigen.
HCV – Hepatitis C virus.

than one agent were rare. One individual had KSHV/HIV-1/HBV while another one had KSHV/HIV-1/HCV. Dual infection with HIV-1 was 2.6%, HBV 4.2%, HCV 2.4% and *T. pallidum* (syphilis) was 1.2%. Importantly, co-infection with HBV, HCV or *T. pallidum* were not associated with increased risk of KSHV infection (Table 1). Although it appeared that HIV-1 infected blood donors were at increased risk of KSHV co-infection POR = 2.8, 95% CI = 1.0–8.0, this trend did not reach statistical significance ($P = 0.06$, Table 1). Importantly, some places of birth showed significant association with KSHV infection. Participants born in the central zone (Dodoma and Singida) had increased risk of KSHV infection POR = 5.7, 95% CI = 1.0–32.5 ($P = 0.048$, Table 1). Likewise, those born in the lake zone (Kagera, Geita, Mwanza and Mara) had significantly increased risk of KSHV infection POR = 6.4, 95% CI = 1.6–25.3 ($P = 0.008$, Table 1). Although these differences are statistically significant, they are based on small numbers ($N = 12$, Central Zone and $N = 35$, Lake Zone). Overall, the prevalence of KSHV in Tanzania is high and consistent with reports from nearby countries.

4. Discussion

Despite the high incidence and prevalence of KS in Tanzania, this is the first study to investigate KSHV prevalence in a cohort derived from Dar es Salaam and to test for associated infectious agents and risk factors of KSHV infection. The cohort sampled was derived from volunteer blood donors in Dar es Salaam. Yet, it was comprised of individuals who have migrated to the metropolitan from throughout Tanzania. Based on recognition that KSHV infection predominantly occurs in childhood in SSA, we assert that this sampling provides a reasonable preliminary estimate of country wide KSHV infection. Consistent with previous reports from Tanzania and nearby countries, the overall Tanzanian KSHV prevalence is high at 56.9%. Enbom et al, reported similar rates of KSHV infection (48%) among urban Tanzanian blood donors nearly two decades ago (Enbom et al., 2002). Another study conducted in rural Tanzania around Lake Victoria at almost the same time-frame reported even higher KSHV seroprevalence (89%) (Mbulaiteye et al., 2003). Ethnicity could be playing a role in risk of KSHV

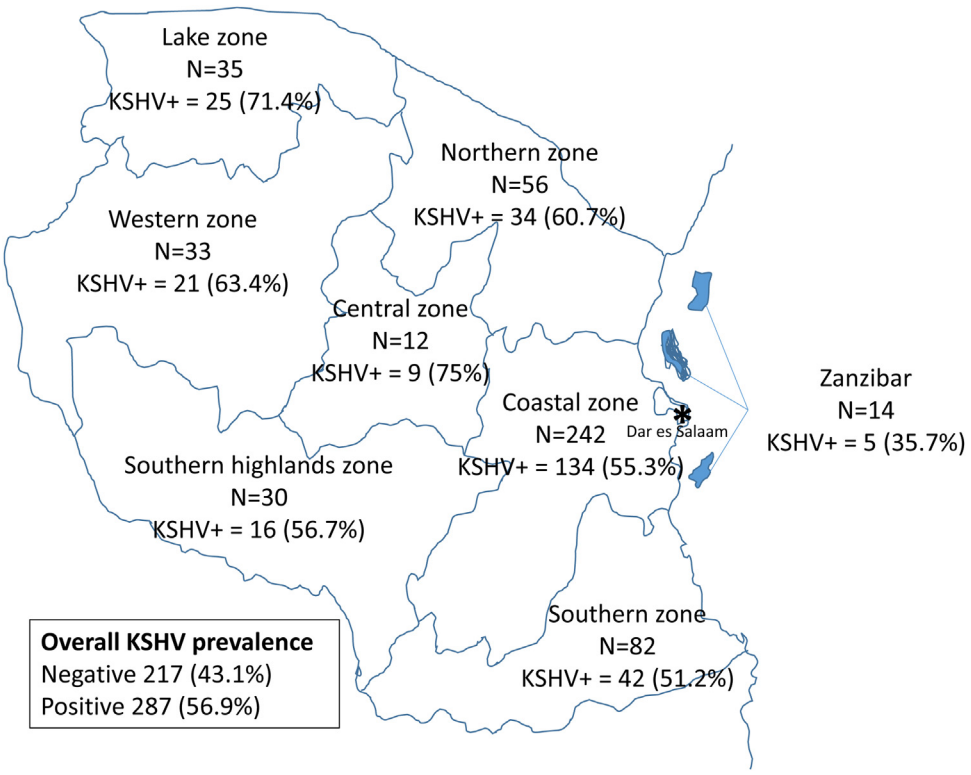

Fig. 1. Schematic representative map of Tanzania showing KSHV prevalence by places of birth.
*Dar es Salaam, sample collection site.

transmission as similarly high rates of KSHV prevalence have been reported in rural Uganda, Xinjiang and Italy (DiGiovanna and Safai, 1981; Franceschi and Geddes, 1995; Zheng et al., 2017; Newton et al., 2018). Differences in assays used, and sampled population groups, could also be the reason for observed differences in KSHV prevalence. High KSHV seroprevalence is directly related to the high prevalence and risk of KS in the region (Globocan, 2018). Despite the relatively small sample number form the Lake Zone in our study ($N = 35$), twenty-five of those (71.4%) were KSHV seropositive, which is consistent with previous studies from the same region (Mbulaiteye et al., 2003; Nalwoga et al., 2019). The observation of disproportionately high KSHV prevalence in persons deriving from around Lake Victoria and from the Central Zone could be due to cultural practices that predispose children to saliva from infected individuals, but this needs to be investigated in greater depth. Premastication of baby foods and chewing of local herbs for wound soothing are common practices in these regions (Butler et al., 2009a; Crabtree et al., 2014). A molecular analysis of KSHV in Zambians households revealed that early KSHV infection in children results from both within and outside the households and from maternal and non-maternal sources (Olp et al., 2013). This suggests that high KSHV burden in adults leads to high transmission to children.

In addition, other factors could be playing a role in KSHV infection leading to high KSHV burden in adults. Farming and fishing activities with extended stay in lake water have all been associated with KS previously, and are very common around Lake Victoria (Ziegler, 1993; Ziegler et al., 1997), but would not be common in the semi-arid dry-farming practices in the Central Zone. Parasitic infections have been associated with high KSHV prevalence in fishing communities on Lake Victoria islands in Uganda (Nalwoga et al., 2019). A recent study of Cameroonian adults also found a positive association between KSHV infection and bathing or standing time in non-treated surface water (Labo et al., 2019). In the Central zone, farming activities and walking with bare feet could contribute to increased KSHV prevalence perhaps due to currently underappreciated environmental exposures that may be unique to that region (Ziegler, 1993; Ziegler et al., 2003). Comprehensive risk factor assessments now appear to be justified to define potential determinants that predispose KSHV infection in these zones.

Although oral shedding of KSHV is independent of HIV-1 co-infection, our group and others have previously reported increased risk of KSHV infection with HIV-1 co-infection (Minhas et al., 2008a; Bagni and Whitby, 2009). The role of HIV-1 in KSHV infection is however, still not clear, as other studies did not find this relationship to be significant (Newton et al., 2018a; Labo et al., 2019 Labo et al., 2019). In this cohort, neither HIV-1, HCV, HBV, nor *T. pallidum* infection was significantly associated with increased risk of KSHV infection, although a trend toward association with HIV-1 was evident. Since KSHV infection is most likely to occur in infancy, whereas most of the other infections assessed are typically acquired through exposure to blood/blood products or sexual activity, the lack of association with KSHV infection appears logical. For example, congenital syphilis is typically lethal. One exception is HBV, which, in other regions, is frequently transmitted congenitally (Wang et al., 2003; Hou et al., 2005; Degli Esposti and Shah, 2011; Borgia et al., 2012). The HBV prevalence in Tanzania is about 6% in adults (Miller et al., 1998) and ranges between 1.8% to 4% in children (Meschi et al., 2010; Muro et al., 2013). Because HBV prevalence in Tanzanian children is on the lower side compared to areas where congenital infection is common, this led us to speculate that acquisition by infants may occur at a low rate and most HBV infections are occurring in adults. This concept needs to be explored further. Differences in geography, ethnicities, economics and HIV-1 prevalence in previous studies could explain the

conflicting observations reported. Similar to other reports in the region, the burden of Hepatitis B and C are still high in the Tanzanian blood donors (Miller et al., 1998; Meschi et al., 2010; Muro et al., 2013; Valerian et al., 2018). Unlike HIV-1 infection, awareness of hepatitis B transmission and its consequences is low in Tanzania (Mueller et al., 2015; Kilonzo et al., 2018). Hepatitis B vaccination of under-fives has only started recently. All these could explain increased prevalence of Hepatitis B infection in this population. Moreover, we found disturbingly high anti-syphilis antibody responses compared to previous studies in the region despite on-going effort to reduce sexually transmitted infections in the country. High rates of syphilis were previously reported during the peak of HIV-1 epidemic in the 90s. In a study conducted in Dar es Salaam blood donors in 1999, HIV-1 and syphilis were at 8.7% and 12.7% respectively (Matee et al., 1999). Increased efforts in community education on safe sex practices and ART, led to a decrease in both HIV-1 and syphilis (3.8% and 4.7% respectively) suggesting the effect of control strategies (Matee et al., 2006). The decoupling of HIV-1 and syphilis infections in this cohort is also contrary to a recent study of blood donors in the northern Tanzania (Valerian et al., 2018). The observed surge in syphilis reported in this study could be an indication of the community being less conscious of preventative measures following reports of declining HIV-1 prevalence or it may suggest a syphilis problem that has become decoupled from HIV-1 infection and transmission. Further studies are needed to clarify risk factors, other than HIV-1, that contribute to or co-associate with syphilis infection in Dar es Salaam.

In most African communities, men are associated with poor health-seeking behaviors (Yeatman et al., 2018). Generally, women are more responsive to health related messages and tend to present to health facilities with earlier stage disease (Yeatman et al., 2018). Consistent with previous studies on blood donors in Tanzania, fewer women volunteered to donate blood in this study (Enbom et al., 2002; Elias et al., 2016; Valerian et al., 2018). Anemia in women has been reported to be one of the main reasons for female reluctance to donate blood (Kumar Meinia and Sawhney, 2016; Paparatnam and Rajani, 2016). Perhaps, fewer women volunteer to donate blood in these studies because of preconceived beliefs that they are anemic as a result of menses (Elias et al., 2016). Well-designed qualitative and quantitative studies are needed to determine barriers of donating blood among Tanzanian women. Under-representation of women, age groups and under-sampling from some Tanzanian provinces in our cohort detracts somewhat from the absolute generalizability of our findings. Nevertheless, the outcomes from this cohort suggest trends that merit further exploration to understand the regional prevalence and risk factors for KSHV infection, and therefore, KS risk.

In summary we report high prevalence of KSHV and syphilis in Tanzanian voluntary non-remunerated blood donors while ruling out several co-infecting agents as risk factors for KSHV infection. As anticipated, prevalence of KSHV infection was high but also revealed focal areas, the Central and Lake Zones, of concentrated prevalence. The observed trends need further exploration and validation in larger studies with more unexplored risk factors to define and mitigate factors that influence the prevalence KSHV infection in Tanzania.

Ethical approval

The study was approved by the review boards of Tanzania National Institute for Medical Research, Ocean Road Cancer Institute and the University of Nebraska-Lincoln (UNL). Investigators at UNL did not interact with human subjects or have access to identifiable data or specimen for research purpose.

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Conflict of interest

All authors declare no conflict of interest.

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