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Prevalence and outcome of HIV-associated malignancies among HIV-infected children enrolled into care at Kilimanjaro Christian Medical Center 2006-2014: A hospital-based retrospective analytical study.

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Abstract

Objective: We aimed to establish the prevalence of HIV-associated malignancies in children attending a care and treatment clinic at Kilimanjaro Christian Medical Centre.

Methods: A retrospective cross-sectional hospital-based study of children who attended a HIV care and treatment clinic between 2006 and 2014. Children aged 2 months to 17 years were eligible for participation. The data on social demographic and clinical characteristics were extracted from the medical record. A multivariate logistic regression model was developed to determine predictors of HIV-associated malignancies.

Results: Medical records from 721 HIV-infected children were reviewed. The median age (IQR) at HIV diagnosis was 5.7 (2.0 to 9.4) years. Among them, 34 (4.7%) had HIV-associated malignancies. The most common (n=24, 70.3%) malignancy was Kaposi's sarcoma. Age at HIV diagnosis was significantly associated with HIV-associated malignancies (aOR=1.2, 95% CI=1.0 – 1.3). Out of 34 patients with HIV-associated malignancies, eleven (32.4%) died. Seven (20.6%) patients reported complete remission from their malignancies, and outcomes for six patients were unknown.

Conclusion: The prevalence of HIV-associated malignancies was high and was associated with late HIV diagnosis. Kaposi's sarcoma was the commonest malignancy. Early HIV diagnosis and treatment in children might reduce HIV-associated malignancies.

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Conflict of interest

The authors declare that there is no conflict of interest for this work.

Keywords

HIV/AIDS; malignancy; care and treatment; children; Tanzania

Introduction

In 2015 an estimated 1.8 million children under the age of 15 years were living with HIV/AIDS worldwide, accounting for 5.0% of all people living with HIV/AIDS (1). Of all children living with HIV, half (50.0%) are living in Eastern and Southern Africa, with 91,000 children less than 14 years with HIV living in Tanzania (2). In 2016 alone, 160,000 children globally were newly infected with HIV, resulting in 18 children acquiring HIV infections every hour (3). Pediatric HIV infection contributes to 8.9% of all new infections and 10.0% of AIDS-related deaths (3).

HIV-associated malignancies are known to increase morbidity and mortality among HIV-infected children (4). Immunosuppression by HIV increases the incidence of certain forms of cancer (5). Patients with AIDS are at increased risk of co-infection with other viruses associated with malignancies such as Human Herpes Virus-8 (HHV-8), Human Papilloma Virus (HPV) and Epstein Barr Virus (EBV) (6). EBV has been found in the tumor cells of Burkitt's lymphoma, other lymphomas, leiomyosarcomas and leiomyoma (7). The co-infection of HIV with other viral infections might be the reason for the observed higher prevalence of HIV-associated malignancies among HIV-infected children, as the co-infecting virus may play a role in the etiology of some malignancies. Despite the association of HIV-related malignancies and child mortality in many low- and middle-income countries including Tanzania, the prevalence of HIV-associated malignancies in children is not known. Conversely, an increase in HIV-associated non-Hodgkin's lymphomas (NHL) and Kaposi's sarcoma (KS) (36%–57%) in children is alarming (8).

Evidence from high-income countries suggests that 2.5% of HIV-infected children had associated malignancies, of which 81% of children had NHL and 8% had KS (9). In a UK cohort of 302 HIV-infected children, nine (3.0%) were diagnosed with HIV-associated malignancies, and NHL was the most prevalent HIV-associated malignancy in this cohort (10). The same has been reported in Africa; for example, in Uganda 1.7% of children had HIV-associated malignancies (4). In this population, more than half (78%) of children with malignancies had KS (4). Sinfield and colleagues in Malawi also found that 84% of HIV-associated malignancies were KS and NHL (11). These data confirm that HIV-associated malignancies in children is a potentially significant problem.

To our knowledge, the prevalence of HIV-associated malignancies in children has not systematically studied in Tanzania, and most published studies are from high-income countries, leaving the real magnitude of the problem in Tanzania unclear. Late presentation, treatment-related toxicity and drug interactions may prevent childhood HIV-associated malignancies from receiving adequate therapy, leading to increased morbidity and mortality. Therefore, establishing the prevalence of HIV-associated malignancies in Tanzania is important to help in planning possible care for the affected children.

Materials and methods

A hospital-based cross-sectional study was conducted between October 2015 and September 2016 at the Kilimanjaro Christian Medical Centre (KCMC) referral hospital. The hospital is among the four-zonal referral hospitals in Tanzania, and it serves seven regions of northern Tanzania. The majority of clients served at KCMC are from the Kilimanjaro Region and neighboring regions such as Arusha, Manyara, Singida and Tanga. The hospital serves over 15 million people living in northern Tanzania, of which about 44% are children below 15 years age.

At KCMC, pediatric HIV care is provided at the Child-Centered Family Care Clinic (CCFCC). The CCFCC was established in 2006 with the aim of providing care to HIV-infected children together with their parents or other infected family members. The Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) has supported this clinic from its start, and patients receive both general pediatric and specialist care accordingly. All children attending the CCFCC are HIV-infected, confirmed by either rapid antibody test for those above 18 months and HIV RNA PCR for those below the age of 18 months. The clinic provides HIV testing, routine monitoring for HIV-infected children including CD4 counts, and liver and renal function. The antiretroviral medications (ARTs) are provided free of charge to all children who are eligible for treatment. In addition to WHO clinical staging, percentage CD4 count for children less than or equal to 5 years, and absolute CD4 count for children older than five years respectively was used to guide ART initiation in this population. However, with the new WHO guidelines in 2016, all HIV-infected children became eligible for ART regardless of age, WHO clinical staging or CD4 count.

Data were extracted from the client care and treatment card (CTC2) of children who attended CCFCC during the study period and their medical record files. In addition, the care and treatment database was used to triangulate client visits and to ensure completeness. Briefly, the files are completed by nurses and physician at each visit. The files record the demographics and HIV-related variables. Additionally, HIV-related and unrelated diagnoses are recorded in the CTC2 card. Participants were considered having cancer if they had a biopsy result confirming cancer, or a fine needle aspiration result or ultrasound scan which led to a clinical diagnosis of malignancy resulting in documented cancer treatment. Outcomes for the malignancy treatment were complete remission (CR), relapse, death, or unknown. Information was extracted from files of patients enrolled into care and treatment between 2006 and 2014. We extracted a total of 721 files of HIV-infected children aged 2 months to 17 years attending care and treatment at the CCFCC, and currently 457 are being actively followed.

Data were extracted from the files into an excel sheet and then transferred to the SPSS version 20 for cleaning and analysis. Categorical variables were summarized using frequencies and percentages, as presented in tables. A multivariate logistic regression analysis was done to determine the independent predictors of HIV-associated malignancies. Results are reported as odds ratios with their 95% confidence intervals (CI), and variables with a p-value less than 0.05 were considered statistically significant.

Ethics approval was obtained from the Kilimanjaro Christian Medical University College Research Ethics and Review Committee, in addition to the Duke University Medical Center Institutional Review Board. Permission to access the files was obtained from the Head of Pediatric and Child Health Department. Confidentiality was maintained throughout the data collection; clients were identified using unique CTC number.

Results

A total of 721 children who attended CTC at KCMC between 2006–2014 were eligible and enrolled. Among the 721 children, slightly more than half (383, 53.1%) were male. The median (IQR) age at HIV diagnosis was 5.7 years (2.0 – 9.4). The median (IQR) CD4 count was 318.5 cells/m³ (151–544) for children above five years, whereas, for the children below five years, the median (IQR) CD4 percentage was 19% (12% - 28%). Nearly one-half of the population were in WHO stage III (327, 45.4%) and 206 (28.6%) in stage IV at the time of the first HIV diagnosis. All HIV-infected children were receiving ART, mostly as first-line non-nucleoside reverse transcriptase inhibitor containing combinations, and only 39 (5.4%) were on protease inhibitor-containing combinations, (Table 1).

Overall, 34 out of 721 patients (4.7%) had HIV-associated malignancies. Among them, nearly two-thirds (64.7%) were male, and the most common HIV-associated malignancy was Kaposi's sarcoma (n=24/34, 70.6%). Table 2 details the prevalence and distribution of HIV-associated malignancies.

After controlling for sex and CD4 count, the age at the first HIV diagnosis had a significant association with odds of HIV-associated malignancy, whereby per a year delay in the HIV diagnosis, the odds of HIV-associated malignancy increased by 1.1 (aOR=1.1, 95% CI=1.0–1.3). It was also observed that female participants had 60% lower odds of having HIV-associated malignancies, but this relationship did not reach statistical significance (p = 0.063), (Table 3).

Chemotherapy was started in 22 (64.7%) patients with HIV-associated malignancies, mostly KS. The most commonly prescribed chemotherapy was a combination of Bleomycin/Vincristine/Doxorubicin (n=8, 23.8%), and one patient with rhabdomyosarcoma had surgery performed.

Of the total 34 children with HIV-associated malignancies, 11 died (32.4%). Of those 11 who died, 8 patients had KS, one both lymphoma and KS, and one each Burkitt's lymphoma and lymphoma. Most of those who died were male (8,72.7%). Five patients died after receiving chemotherapy, while another 6 died before chemotherapy was initiated. Seven patients had complete cancer remission (20.6 %); among them 4 had KS, 2 had Burkitt's lymphoma and 1 had nephroblastoma. One patient had KS relapse following possible complete remission. Outcomes for 15 cancer patients remained unknown; of these, 8 were given chemotherapy and 2 had surgery but there was no documentation of what happened after these interventions. For one KS patient, it was only documented that she was not given chemotherapy because was unstable. For the remaining patients, 2 were lost to follow up, 1 was transferred out and the last one absconded from the hospital.

Discussion

This study aimed to establish the prevalence of HIV-associated malignancies, associated factors, and the outcomes. In the population of HIV-infected children receiving care at a referral hospital in northern Tanzania, the prevalence of HIV-associated malignancy was found to be 4.7%. Of note, this reported prevalence is considered high compared to the currently available literature. For example, one study in Uganda reported a prevalence of 1.7% (4). One explanation for the observed high prevalence is that KCMC was the first to start a pediatric HIV clinic in Tanzania, and children with complications were referred to KCMC from all regions around the catchment area reflecting a referral bias.

Additionally, suspected cases of KS from the peripheral clinics were referred to the KCMC Regional Dermatology Training Center for further management, and were sent to the CCFCC for HIV care and treatment. Further, this study enrolled children who were diagnosed between 2004 and 2014, while the universal access to ART for eligible patients only started in 2007. At that time KCMC was among the few hospitals to provide ART services, and patients including children were referred to CCFCC for HIV care and ART initiation. Each of these factors may have contributed to referral bias, which could elevate the prevalence of HIV-associated malignancies. Additionally, we observed that the children receiving care at KCMC were probably among the long-term survivors and the majority were diagnosed at a late stage (stage III or IV) of HIV disease, and HIV-associated malignancies might have been their first HIV presenting signs. However, it is hoped that with current efforts to prevent mother to child transmission, and early infant diagnosis and initiation of ART, the prevalence of HIV-associated malignancies in children may decrease.

Overall, 24 children out of 34 who were diagnosed with HIV-associated malignancies had Kaposi's sarcoma. As a result of having a Regional Dermatology Center and the first pediatric HIV clinic in the region, most of the cases with cutaneous HIV manifestations were referred to KCMC, which might explain the higher rate of KS observed in this study. Several studies in low-income countries reported similar results such as in Malawi where the prevalence of KS in HIV-associated malignancies was 84% (11), in a cohort of HIV-infected children in South Africa where KS was the leading HIV-associated malignancy (12), and in Uganda where KS was reported in 78% of children with HIV-associated malignancies (4). These observations are in contrast to high-income countries where NHL is the most common HIV-associated malignancy (9,10). Compared to the general pediatric population in northern Tanzania, non-Hodgkin lymphomas particularly Burkitt's lymphoma are the most common tumors. For example, a study by Schroeder and colleagues in a general pediatric population reported a relative proportion of 18% for Burkitt's lymphoma, 14% for Wilm's tumor, 11% for retinoblastoma, and 4% for KS (13).

Age of the child at the time of HIV diagnosis was found to be an independent predictor of HIV-associated malignancies. Almost all children included in our study acquired the HIV perinatally, but diagnosis was very delayed. Delaying HIV diagnosis among this pediatric population was significantly associated with HIV-associated malignancies, possibly due to immune suppression and high viral load. Each of these factors could lead to increases in the risk of developing malignancy, especially with delays in HIV care initiation. In this cohort of

children, the median age at HIV diagnosis was 5.7 years. Similar to our findings, one review reported a significant association between the time of HIV diagnosis and HIV-associated malignancies (14). Late initiation of ART might have contributed to the development of malignancies. In our study the median age at HIV diagnosis was 5.7 years, while mean age at malignancy diagnosis was 8.2 years. For some children, the malignancy diagnosis is the one which triggered providers to request HIV testing and ART could not have been initiated earlier. Following the malignancy diagnosis, they were initiated on ART because of their advanced clinical stage. Both late diagnosis and late initiation of ART contributed to the high prevalence of HIV-associated malignancies. However, with the current interventions including early infant diagnosis, and test and treat policy, the prevalence of HIV associated malignancies is likely to decline.

The malignancy treatment outcomes in this population were poor, with 32.4% of children dying of their HIV-associated malignancy, including approximately a quarter who had KS. The poor treatment outcomes in this cohort of children may be attributed to the late presentation of both HIV and/or their HIV-associated malignancy, which led to challenges in initiating the chemotherapy, (some children died before chemotherapy was initiated because they came in critical condition). These outcomes are similar to the reported to the 50% survival rate reported from the Upendo Ward at the Muhimbili National Hospital in the same period during the rollout of universal HIV care.

Limitations

A number of participants (21/34) had no biopsy or fine needle aspiration cytology results to confirm clinical diagnosis of malignancy. Since there were no confirmatory results, this shortcoming might have overestimated their true prevalence. On the contrary, since Tanzania had one specialized cancer institute during the period of our study, probably children with or suspected to have cancer were referred there, and this might have underestimated the observed prevalence. This factor may have been important in our study where relatively few cases of NHL were observed, due to limitations in chemotherapy and supportive care, and a referral bias to the single specialized center. In contrast, as a referral hospital with specialized dermatology care, we might have overestimated the observed prevalence of KS. In addition, the outcomes of children who were lost to follow up were not known.

Despite these limitations, the observed prevalence gives a baseline for future estimation of the prevalence and treatment outcomes in relation to the improved early diagnosis and treatment services available both for HIV and malignancies.

Conclusion

We found a high prevalence of HIV-associated malignancy in this pediatric HIV-infected population, with Kaposi's sarcoma being the most prevalent cancer. Age of the child at HIV diagnosis was an independent risk factor for developing HIV-associated malignancies. Early diagnosis and initiation of ARVs for children with HIV may be important in prevention of HIV-associated malignancy.

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Table 1:

General characteristics of HIV-infected children enrolled in CTC at KCMC from 2006–2014 (n=721)

Variable	n (%)
Diagnosis age (years), median (IQR)	5.7 (2.0 – 9.4)
Sex	
Male	383 (53.1)
Female	338 (46.9)
CD4 count	
CD4 counts, median (IQR) (>5 years)	318.5 (151 – 544)
CD4 percentage, median (IQR) (< 5 years)	19% (12% - 28%)
WHO stages^a	
Stage I	27 (3.8)
Stage II	160 (22.2)
Stage III	327 (45.4)
Stage IV	206 (28.6)
ARV^b	
NNRTIs	682 (94.6)
PIs	39 (5.4)

^aWHO clinical stage at the time of HIV diagnosis^bARVs drug patient were on the last visit seen at the clinic prior data collection. All children were on NRTIs.

Table 2:

Proportion of children with HIV-associated malignancies and their clinical presentations (n=721)

Characteristics	Total	n (%)
Prevalence		
Overall	721	34 (4.7)
By sex		
Male	384	22 (5.7)
Female	337	12 (3.7)
By cancer type		
Kaposi Sarcoma	721	24 (3.3)
Lymphoma	721	3 (0.4)
Burkitt's Lymphoma	721	4 (0.6)
Nephroblastoma	721	1 (0.1)
Rhabdomyosarcoma	721	1 (0.1)
Lymphoma and lymphadenopathic KS	721	1 (0.1)

*
Some children had more than one presentation

Table 3:

Bivariate and multivariate analysis of Factors associated with HIV-associated malignancies among HIV-infected children enrolled into care at KCMC

Variables	HIV associated malignancies		Univariate analysis		Multivariate analysis	
	Yes n (%)	No n (%)	cOR (95%CI)	p-value	aOR (95%CI)	p-value
Diagnosis age (years)	8.2 (3.9 – 12.1) ^a	5.6 (1.9 – 9.3) ^a	1.1 (1.0 – 1.2)	0.019	1.2 (1.0 – 1.3)	0.012
Sex						
Male	23 (6.0)	361 (94.0)				
Female	11 (3.3)	326 (96.7)	0.5 (0.3 – 1.1)	0.090	0.4 (0.2 – 1.0)	0.063
Immunodeficiency by CD4 (<i>n=552</i>)						
Not significant	6 (4.4)	133 (95.7)				
Mild	3 (3.5)	83 (96.5)	0.8 (0.2 – 3.3)	0.758	0.7 (0.2 – 3.0)	0.656
Advanced	7 (6.2)	106 (93.8)	1.5 (0.5 – 4.5)	0.505	1.3 (0.4 – 4.2)	0.606
Severe	7 (3.3)	209 (96.7)	0.7 (0.2 – 2.3)	0.611	0.7 (0.2 – 2.2)	0.570

^aMedian (Interquartile range)

Table 4:

Management of HIV-associated malignancies (N = 34)

<i>Kaposi Sarcoma (n=24)</i>	n
Chemotherapy (Bleomycin, Vincristine, Cytostatic)	1
Chemotherapy (Bleomycin, Vincristine, Doxyrubicin)	8
Chemotherapy (Bleomycin, Vincristine)	7
Chemotherapy (Vincristine)	2
Chemotherapy (Bleomycine, Vincristine, Methotraxate)	1
No treatment (Died, unstable, TFO)	5
<i>Lymphoma (n=3)</i>	
No treatment (Died)	1
Surgery	1
Chemotherapy (Cyclophosphamide, Vincristine, Methotraxate)	1
<i>Burkitt's Lymphoma (n=4)</i>	
Chemotherapy (Allopurinol, Cyclophosphamide, Vincristine, Methotraxate)	2
No treatment (Died)	1
Referred to MNH for chemotherapy	1
<i>Nephroblastoma (n=1)</i>	
Chemotherapy (Dactinomycin + Vincristine)	1
<i>Rhabdomyosarcoma (n=1)</i>	
Surgery	1
<i>Lymphoma and lymphadenopathic KS (n=1)</i>	
Referred to MNH for chemotherapy	1
MNH=Muhimbili National Hospital	