Brief Report

The association between skin cancer and HIV infection

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Abstract

Background: People affected by Human Immunodeficiency Virus (HIV), are burdened by a higher risk of developing malignancies including non-melanoma skin cancer (NMSC) and melanoma skin cancer.

Objective: To evaluate the association of HIV with melanoma and NMSC at a University Hospital.

Methods: This is a cross-sectional retrospective study of HIV-infected and a matched comparison group, analyzing the associations between skin cancer and HIV infection.

Results: Compared to the HIV-uninfected, HIV-infected had 80% association with skin cancer (CI 95%: 1.3-2.4, P = 0.001) The risk was 45-fold higher by patients" age (CI 95%: 3.3-15.9: P = 0.001). When adjusted for patient age, sex and race, the risk was 6.4 fold ligher of having cancer if compared to the others (CI 95%: 49-84, P = 0.001). Melanoma was not found in HIV-infected.

Conclusion: With this study, we have demonstrated that HIV-infected patients have an increased risk of BCC and SCC. Preventive dermatologic management is pivotal in the care of immunosuppressed patients. These patients must undergo the dermatological examination annually and should receive extensive counseling regarding sun avoidance, use of sunscreens,and sun-protective clothing.

Key words: HIV infection, basal cell carcinoma, squamous cell carcinoma, melanoma

Plain Language Summary

Skin cancer accounts for most malignancies across the globe, with more than 1.5 million new cases estimated in 2021. People affected by HIV are burdened by a higher risk of developing malignancies such as non-melanoma skin cancers and malignant melanoma. This study, from Brazil, aimed to evaluate the association of HIV with skin cancer at a University Hospital. The study comprised 594 HIV-infected (1.6%) and 37,570 (98.4%) HIV-uninfected persons (n = 38.164), 1601 nonmelanoma skin cancer (43 HIV-infected vs 1558 HIV uninfected) and 107 cutaneous melanomas (all of them HIV-uninfected). We have demonstrated that HIV-infected patients have an increased risk of squamous cell carcinoma and basal cell carcinoma. Squamous cell carcinoma has the strongest association, with statistical significance and prevalence ratio of 5.1 for HIV-infected when compared to HIV-uninfected. Preventive dermatologic management is pivotal in the care of immunosuppressed patients. These patients must have a dermatological examination annually and should receive extensive counseling regarding sun exposure, use of sunscreens, and sun-protective clothing.

Introduction

The advent of antiretroviral therapy has markedly extended the survival rates of patients with human immunodeficiency virus (HIV) leading to suppression, though not eradication of HIV. Cancer has become a growing problem, representing a leading cause of morbidity and mortality among people living with HIV.[1] A large number of worldwide studies have shown that HIV infection raises the risk of many non-AIDS defining cancers, including melanoma and non-melanoma skin cancer (NMSC).[2,3]

Non-melanoma skin cancer (NMSC), defined as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is the most common malignant condition in the world.[4] Among immunocompetent individuals, BCCs are more common than SCCs. However, among

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immunocompromised persons, SCCs predominate over BCCs.[5,6]

The HIV-infected population has a risk of developing BCC and SCC that is increased 2-fold and 5-fold, respectively, over the general population. The risk of NMSC, especially SCC, increases further in patients with poorly controlled disease, who are subsequently more immunosuppressed (CD4 <200 cells/mL and/or HIV viral load of 10,000 copies/mL).[5,7–11]

The incidence of melanoma in HIV-infected patients is 2.6 times higher as compared to non- HIV patients, which reflects both a decreased efficiency of the host immune response in eliminating potentially malignant cells and an improvement in the treatment of HIV patients - because of the development of new antiretroviral agents. The latter prolongs the survival of the infected patients increasing the time of immunodeficiency and the possibility of tumour development.[12–15]

Methods

Following the Gaffree & Guinle University Hospital–Rio de Janeiro Medical Ethics Committee (CAAE 08945 019.0.0000.5258), we carried out this cross-sectional retrospective study of HIV patients and a matched comparison group, analysing the associations between skin cancer and HIV infection.

Our study used the computerised database of GGHU, comprising 38,164 subjects from 2005–2018: 594 HIV-infected and 37,570 HIV-uninfected patients. The search terms were: ("HIV" or "human immunodeficiency virus" or "HIV-infection" or HIV-positive) and ("BCC" or "basal cell carcinoma") and ("SCC" or "squamous cell carcinoma") and ("melanoma and non-melanoma skin cancer"). Laboratory databases were requested to obtain CD4 levels in the HIV-infected group, and biopsy samples of all HIV infected patients were reviewed. The data collected were grouped into plain Microsoft Excel® spreadsheets and subsequently converted into the Stata®, version 15.1 (serial: 301506206729), to perform the statistical analysis.

The inclusion criteria were patients treated at Gaffree & Guinle University Hospital between 2005 and 2018, aged 18 years or older and with a histopathological diagnosis of skin cancer that includes melanoma, BCC and SCC, both in HIV-infected and HIV-uninfected. The exclusion criteria were patients aged less than 18 years, histopathological diagnosis other than melanoma or BCC and SCC or exclusively extracutaneous melanoma, BCC or SCC.

The study characteristics were HIV-infected or HIV-uninfected, skin cancer (yes or no), BCC (yes or no), SCC (yes or no), sex (male or female), age, categorical (years): 18–49, 50–64 or >64 years old, race/colour (white or medium/black), cancer location (head and neck, trunk, genitals, upper limbs or lower limbs).

The exposure considered was the presence of HIV, and the outcome was skin cancer. For this, the distribution of the absolute and relative frequencies of the categorical variables with cancer was carried out. The chi-square test was also applied, with a significance level of 5.0%.

The estimated association measure for exposure (HIV) and outcome (skin cancer) was the gross and adjusted prevalence ratios, with respective 95.0% confidence intervals. Logistic regression was used for this calculation, then the conversion of odds ratio was performed due to prevalence through the Zhang[16] and by the odds risk command in Stata® in version 15.1 (serial: 301506206729). Besides, the Hosmer-Lemeshow test[17] assessed the quality of the adjusted model, considered adequate when the *P*-value was higher than 0.10.

Results

The study comprised 594 HIV-infected (1.6%), 37570 (98.4%) HIV-uninfected persons (n = 38164), 1601 NMSC (43 HIV-infected vs 1558 HIV-uninfected) and 107 cutaneous melanomas (all of them HIV-uninfected). The mean age was 53.6 years (standard deviation ± 16.4), and in the skin cancer group, it was 66.9 years (standard deviation ± 13.7). In those who did not have skin cancer, it was 52.9 years (standard deviation ± 16.2). The duration of HIV disease in all NMSC patients was greater than 10 years (the mean duration was 12.8 years). Most HIV-infected were using antiretroviral therapy (93.2%), the main antiretroviral regimen in the first years of the study was AZT/3TC+EFZ. As of 2013, the most used antiretroviral regimen was TNF+3TC+EFZ.

We summarised the study characteristics in Table1. The NMSC prevalence in males was 697 (5.7%) and, in females, 716 (3.2%) vs NO-NMSC 11.560 (94.3%) male and 21.505 (96.8%) female. The age group most affected with NMSC was

Table 1: Characteristics of the study population (n = 38164)

Characteristics	NMSC (%)	NO-NMSC (%)
Number of cases	1558 (4.1)	36606 (95.9)
Sex*[3686]		
Male	697 (5.7)	11560 (94.3)
Female	716 (3.3)	21505 (96.8)
Age, categorical (years)*[13425]		
18–49	129 (1.3)	9567 (987.7)
50–64	331 (4.0)	7836 (96.0)
>64	675 (9.8)	6201 (90.2)
Race/colour*[25518]		
White	646 (7.9)	7494 (92.1)
Medium/Black	94 (2.1)	4412 (97.9)
HIV		
HIV-infected	43 (7.2)	551 (92.8)
HIV-uninfected	1515 (4.0)	36055 (96.0)

NMSC: non-melanoma skin cancer; NO-NMSC: No non-melanoma skin cancer

*Number of lost information for each characteristic

Table 2: Association between HIV positive and skin cancer (*n* = 38.164)

CANCER	PR	CI 95%	*P*	aRP*	CI 95%	*P*	aRP**	CI 95%	*P*
BCC	1.1	0.7 a 1.7	0.651	2.8	1.9 a 4.2	<0.001	4.4	2.9 a 6.3	<0.001
SCC	5.1	3.3 a 7,8	<0.001	12.3	7.9 a 18.7	<0.001	22.7	14.2 a 34.6	<0.001
BCC&SCC#	1.8	1.3 a 2.4	<0.001	4.4	3.3 a 5.7	<0.001	6.4	4.9 a 8.1	<0.001

BCC: Basal cell carcinoma; SCC: Squamous cell carcinoma; PR: Prevalence ratio; CI: Confidence interval; aRP*: Prevalence ratio when adjusted for patient age; aRP**: Prevalence ratio when adjusted for patient age, sex, and race. BCC&SCC#: Basal cell carcinoma and squamous cell carcinoma, Model quality (2): BCC (*0.22; **0.12); SCC (*0.19; **0.21); BCC&SCC (*0.19; **0.21)

>64 years old 675 (9.8%) vs 18–49 years old in the NO-NMSC group 9567 (98.7%). White individuals were 646 (7.9%) and medium/black individuals were 94 (2.1%) in NMSC group vs 7494 (92.1%) and 4412 (97.9%) in NO-NMSC group. HIV-infected group had 43 (7.2%) individuals with NMSC vs 551 (92.8%) NO-NMSC. HIV-uninfected had 1515 (4.0%) individuals with NMSC vs 36.055 (96.0%) NO-NMSC.

Among people who had BCC and HIV, the involvement of anatomical sites varied, with 14 (66.6%) occurring on the head, followed by the neck 5 (23.8%) and lastly the abdomen in 1 (4.7%). The prevalence of BCC in sun-exposed areas in 20 (95.2%) patients confirms the important role of ultraviolet radiation in the genesis of this tumour.

The most common site of SCC was the genital region in 15 (68.2%), followed by the trunk 2 (9.1%). In 5 (22.7%) patients, the lesions were on the face, lips, sacral region or upper limbs. Biopsy samples were analysed, and microscopy with H&E staining detected genital cases with some histopathological alteration suggestive of human papillomavirus infection 8 (54.5%), such as koilocytotic atypia, cytopathic alterations of probable human papillomavirus-like viral lesion or Bowenoid papulosis.

Compared to the HIV-uninfected, HIV-infected had 80% association with skin cancer (CI 95%: 1.3–2.4; $P < 0.001$). The risk was 4.5-fold higher by patients' age (CI 95%: 3.3–5.9; $P < 0.001$). When adjusted for patient age, sex and race, the risk was 6.4-fold higher of having cancer if compared to the others (CI 95%: 4.9–8.4; $P < 0.001$) [Table 2]. In addition to the crude analysis of the association between HIV and NMSC, calculations were adjusted for age, sex and race/colour and there was no impact of these confounding factors on the outcome of our study.

Squamous cell carcinoma (SCC) had the strongest statistical association, with prevalence ratio of 5.1 for HIV-infected compared to HIV-uninfected (CI 95%: 3.3–7.8; $P < 0.001$). When adjusted for patient age, sex and race, the risk of having cancer was 22.6-fold higher (CI 95%:14.5–35.4; $P < 0.001$). Our hospital is a referral centre for patients with HIV infection, so all our NMSC HIV-infected patients were receiving antiretroviral therapy.

We found 119 cases of cutaneous melanoma, but none of these individuals had HIV, so it was not possible to carry out a study with its characteristics. The database did not contain other information that could impact the study, such as a history of sun exposure or use of tanning beds.

Discussion

In 2021, 37.7 million people were living with HIV.[18] A large number of worldwide studies have shown that the HIV-infected population has an increased risk of developing BCC and SCC as compared to the general population.[5,7,8] Our study presents the clinical features and epidemiology of HIV-infected with NMSC to better understand this condition.

This retrospective cross-sectional study of 38164 pathology records from Gaffree & Guinle University Hospital showed 1558 (4.1%) NMSC and 107 (0.3%) cutaneous melanoma. Forty three of the NMSC patients were HIV-infected (21 BCC and 22 SCC); however, none of the HIV patients had melanoma. We believe that this was due to the rarity of this tumour. Also, our hospital is not a referral centre for cancer. The number of new cases of melanoma described in 2018 in the Brazilian territory was 6260, so it is possible to understand its rarity in our sample (594 HIV-infected).[19] We used Gaffree & Guinle University Hospital laboratory databases to obtain laboratory test results (CD4 count), but we found no association between CD4 count <200 cells and large or more severe tumours.

The HIV-infected population has a risk of developing BCC and SCC that is increased 2-fold and 5-fold, respectively, of the general population.[5,7–9] The results of our study were similar to the data in the literature, and HIV-infected patients with NMSC had a higher risk of tumour development compared to HIV-uninfected in the same hospital. SCC had the strongest association.

The overall sex ratio among this sample favoured females. However, when we selected HIV-infected individuals with NMSC, the majority (67.4%) were men. This was probably due to the greater number of cases of HIV infection being in men. The age group with the highest incidence of NMSC was >64 years, whereas the most prevalent age range in HIV-infected patients was 50–64 years, suggesting that the virus may influence the development of NMSC.

Both groups had a preponderance of white race. The prevalence of BCC in sun-exposed areas 20 (95.2%) confirms the essential role of ultraviolet radiation in the genesis of this tumour. In this patient group, the higher number of SCC

diagnosed in the genital area 15 (68.2%) endorses the role of the human papillomavirus in the genesis of SCC.

HIV-infected have a higher risk of contracting human papillomavirus, including oncogenic viruses, due to high risk behaviour and immunosuppression.[20,21] Microscopy with H&E staining detected 8 (54.5%) cases with histopathological findings suggestive of human papillomavirus infection, such as koilocytotic atypia, cytopathic alterations of probable human papillomavirus-like viral lesion or diagnosis of bowenoid papulosis.

Many Gaffree & Guinle University Hospital patients take antiretroviral therapy regularly, which may explain the high CD4 cell count of these individuals. Considering that this Hospital is a quaternary hospital that promotes prevention campaigns like the national campaign for the prevention of skin cancer by the Brazilian Society of Dermatology annually—these patients may be protecting themselves, so we believe that this can influence the results.

The advent of antiretroviral therapy has markedly extended the survival rates of patients with HIV, so cancer has become a growing problem, including melanoma and non-melanoma skin cancer. With this study, we have demonstrated that HIV-infected patients have an increased risk of BCC and SCC. Since there was no melanoma diagnosis in the HIV-infected group, we cannot make a solid conclusion regarding the risk of this tumour in these individuals.

Preventative dermatologic management is pivotal in the care of immunosuppressed patients. These patients must have a dermatological examination annually and should receive extensive counselling regarding sun exposure, use of sunscreens and sun-protective clothing.

Further studies are needed to compare different geographical areas in the city of Rio de Janeiro and the Brazilian territory.

As a limitation, we can mention that the database did not contain other information that could impact the study, such as a history of sun exposure or tanning bed use.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Conflict of interest

There are no conflicts of interest.

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