

Malignancies in individuals living with HIV/AIDS

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ABSTRACT

Background. The incidence of malignancy is heightened in individuals infected with Human Immunodeficiency Virus (HIV). Despite a decrease in the incidence of HIV infections resulting from antiretroviral therapy (ART), the prevalence of HIV-associated malignancies remains substantial.

Objective. Our objective was to examine the types of cancer that initially manifest in individuals infected with HIV or emerge during their subsequent observation period.

Material and method. The study conducted a retrospective analysis of demographic characteristics, malignancy types, presenting symptoms, mode of transmission, HIV-RNA levels, and CD4/CD8 ratios in individuals living with HIV who developed malignancies and were under follow-up at the Infectious Diseases Polyclinic between October 2018 and December 2022.

Results. Out of the 465 patients who were monitored during the study, 27 individuals (5.8%) were diagnosed with various malignancies. Among these patients, 22 (81%) were men and 5 (19%) were women. The average age of the patients ranged from 45.87±9.12 years. Among the patients, 17 (63%) were married and 10 (17%) were single. In terms of education, 16 patients (59.3%) had completed primary school, 7 patients (25.9%) were university graduates, and 4 patients (14.8%) had completed high school. The mode of HIV transmission in all patients was through sexual intercourse. The reasons for testing varied, with 8 patients (29.7%) being tested due to fever, 6 patients (22.2%) before undergoing surgery, 3 patients (11.1%) due to weight loss, and 2 patients (7.4%) tested for reasons such as job application, diarrhea, pre-blood donation, lymphadenomegaly, and dysphagia. The most common types of malignancies observed in the patients were non-Hodgkin's lymphoma (NHL) with 11 cases (40.7%), followed by Kaposi's sarcoma (KS) with 5 cases (18.5%), and cervical carcinoma with 3 cases (11.1%).

Conclusion. The incidence of cancer is higher among individuals with HIV. There is a need to enhance the awareness among both healthcare providers who specialize in HIV care and those who do not.

Keywords: HIV-AIDS, CD4/CD8 ratio, Kaposi's sarcoma, non-Hodgkin lymphoma

INTRODUCTION

HIV infection first emerged in Central Africa during the 1970s and later escalated into an epidemic in

Sub-Saharan Africa in the late 1970s. By the 1980s, it had evolved into a pandemic. Initially believed to predominantly affect men who have sex with men

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(MSM), HIV has now become a global public health concern that can impact individuals from all walks of life. In Turkey, according to the official records of the Ministry of Health, an estimated 32,000 people were reported to be living with HIV as of the end of 2021, with approximately 26,000 of them being men [1]. Notably, individuals living with HIV have a heightened susceptibility to cancer development [2]. Acquired Immune Deficiency Syndrome (AIDS) is associated with defining malignancies such as KS, NHL, and cervical cancer [3]. The etiology of these AIDS-related cancers often involves oncogenic viruses, including Epstein-Barr Virus (EBV), Human Herpes Virus-8 (HHV-8), and Human Papillomavirus (HPV). The compromised immune system resulting from a decreased number of CD4 T lymphocytes fails to effectively combat viral infections, predisposing individuals to malignancies. More than 50% of lymphomas observed in AIDS patients are linked to EBV, while HHV-8 is associated with KS, Primary Effusion Lymphoma, and multicentric Castleman disease. Furthermore, EBV is implicated in Hodgkin lymphoma and non-Hodgkin lymphoma [4]. The introduction of Antiretroviral Therapy (ART) in 1996 significantly prolonged the lifespan of people living with HIV/AIDS. ART inhibits viral replication, boosts immune function, and reduces mortality. However, even in the era of ART, individuals with HIV remain at greater risk of developing cancer compared to their healthy counterparts. Approximately 10-20% of all deaths among people living with HIV are attributed to cancer [5,6].

A comprehensive meta-analysis study that encompassed over 400,000 patients demonstrated that individuals with HIV have an elevated risk of developing lymphoma, with this risk ranging from 23 to 353 times greater compared to those without HIV [7]. A study conducted in France revealed that the incidence of HIV-related NHL was 117 times higher in the pre-ART period (1992-1996) and nine times higher in the post-ART period (2005-2009) when compared to the general population [8]. Early in the AIDS pandemic, an alarming number of KS cases were observed, leading to its inclusion as one of the AIDS-defining diseases by the Centers for Disease Control and Prevention (CDC). Subsequently, NHL and cervical carcinoma were also added to the list. AIDS-related KS tends to be more prevalent in individuals who engage in sexual intercourse, particularly men. Notably, there has been a recent increase in the incidence of KS among African American men living with HIV [9,10].

MATERIAL AND METHOD

Our study aimed to investigate the dermatographic characteristics (gender, age, marital status, education level), HIV transmission route, CD4/CD8

ratio at initial presentation, HIV-RNA levels, and the types of malignancies among HIV/AIDS patients with malignancies who had been receiving care at the Infectious Diseases Outpatient Clinic between October 2018 and December 2022. We conducted a retrospective analysis of patient files, specialized follow-up forms, and data from the hospital automation system. The study included patients who had a serologically confirmed diagnosis of HIV/AIDS (HIV-1 RNA >500 copies/mL) based on the Artus HIV-1 QS-RGQ test (QIAGEN LTD, Crawley, UK). We only included patients who had malignancies and were aged 18 years or older. Categorical variables were reported as frequency and percentage, while continuous variables that did not exhibit a normal distribution were presented as the median.

The study received approval from the Ethics Committee of Health Sciences University Kartal Dr. Lütfi Kırdar City Hospital on January 25, 2023, with decision number 2022/514/242/17.

RESULTS

Our study included a total of 27 participants, comprising 22 males (81%) and 5 females (19%). The participants had a mean age of 45.87 ± 9.12 years. Among them, 17 (63%) were married, while 10 (17%) were single. In terms of education, 16 (59%) had completed primary school, 7 (56%) were university graduates, and 4 (15%) had completed high school.

The primary mode of transmission observed in all patients was sexual intercourse (100%). Among these cases, heterosexual sexual intercourse was the most common mode of transmission, accounting for 60.2% of reported cases. Regarding the reasons for testing, 29.7% of patients were tested for fever, 22.2% for preoperative preparation, 11.1% for weight loss, and 7.4% each for job application, diarrhea, blood donation, lymphadenomegaly, and dysphagia. The malignancies observed in the study population included 47% NHL, 17% KS, 10% carcinoma of the cervix, and 7% each of anal carcinoma and lung cancer.

In patients diagnosed with NHL, the median HIV-RNA value was recorded at 182,563 copies/ml, while the median CD4/CD8 ratio amounted to 0.23. Meanwhile, for patients with KS, the median HIV-RNA level was found to be 71,900 copies/ml, accompanied by a median CD4/CD8 ratio of 0.19. Similarly, among individuals with invasive cervical cancer, the median HIV-RNA was observed at 466,540 copies/ml, and the median CD4/CD8 ratio stood at 0.76. Lastly, in cases of anal carcinoma, the median HIV-RNA was determined to be 247,875 copies/ml, while the median CD4/CD8 ratio reached 0.31 (Table 1).

TABLE 1. Demographic and clinical characteristics of the cases

Type of cancer	Gender (n, %)	Age (years)	Marital status	Education Level	HIV RNA	CD4/CD8 ratio	Reason for test request	Total (n =27) %
NHL	M (n=2) (18%) F (n=9) (82%)	Median: 42 SD+/- 11	Unmarried (n=2) (18%) Married (n=9) (82%)	Primary School (n=2) (18%) High School (n=2) (18%) University (n=2) (18%)	182,563 copies/ml	0.23 SD+/- 0.4	Weight loss (n=3) (27%) Fewer (n=2) (18%) LAP (n=2) (18%) Diarrhea (n=1) (9%) Before invasive procedure (n=2) (18%)	11-47%
Kaposi's sarcoma	M (n=4) (80%) F (n=1) (20%)	Median: 38 SD+/- 12	Unmarried (n=2) (40%) Married (n=9) (60%)	Primary School (n=5) (100%)	71,900 copies/ml	0.19 SD+/- 0.5	Before invasive procedure (n=3) (60%) Diarrhea (n=2) (40%)	5-17%
Cervix CA	F (n=3) (100%)	Median: 38.3 SD+/- 7	Unmarried (n=1) (33%) Married (n=2) (67%)	Primary School (n=2) (67%) University (n=1) (33%)	466,540 copies/ml	0.76 SD+/- 0.4	Before invasive procedure (n=3) (100%)	3-10%
Anal CA	M (n=2) (100%)	Median: 59.3 SD+/- 7	Married (n=2) (100%)	Primary School (n=1) (50%) University (n=1) (50%)	247,875 copies/ml	0.31 SD+/- 0.05	Blood Donation (n=1) (50%) Before invasive procedure (n=1) (50%)	2-7%
Lung CA	E (n=2) (100%)	Median: 55.5 SD+/- 0.7	Unmarried (n=1) (50%) Married (n=1) (50%)	Primary School (n=2) (100%)	97,795 copies/ml	0.21 SD+/- 0.12	Before invasive procedure (n=2) (100%)	2-7%
Breast CA	F (n=1) (100%)	45	Married (n=1) (100%)	Primary School (n=1) (100%)	28,400 copies/ml	0.1	Fewer (n=1) (100%)	1-3%
Rectum CA	M (n=1) (100%)	24	Married (n=1) (100%)	High School (n=1) (100%)	101,737 copies/ml	0.2	Before invasive procedure (n=1) (100%)	1-3%
Larynx CA	M (n=1) (100%)	66	Married (n=1) (100%)	High School (n=1) (100%)	412,752 copies/ml	0.1	Job application (n=1) (100%)	1-3%
Prostate CA	M (n=1) (100%)	55	Married (n=1) (100%)	Primary School (n=1) (100%)	213,597 copies/ml	0.1	Job application (n=1) (100%)	1-3%

NHL: non-Hodgkin Lymphoma, CA: Cancer, M: Male, F: Female

DISCUSSION

According to the findings from the National Cancer Institute's HIV/AIDS Cancer Matching Study, the incidence of cancer among individuals living with HIV primarily consisted of Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and Hodgkin's lymphoma. Less commonly observed were cervical, anal, and lung cancer cases [11].

In a study conducted in Turkey from 2016 to 2017, it was reported that over 42% of individuals living with HIV were identified in Istanbul [11]. This information aligns with the data obtained from the Ministry of Health in 2018, which indicated that the majority of diagnosed and registered HIV-positive individuals in Turkey fell within the 25-34 age range, with males comprising approximately 79.9% of the cases [12]. In our specific study, all of the patients were based in Istanbul, similar to the national data, and 81% of them were male. The mean age of the patients was estimated to be 45.87 years, and it was

observed that those diagnosed with cancer tended to be older.

In our country, it is mandatory to undergo anti-HIV testing in various situations, including before blood and organ donation, prior to surgery, for sex workers, before marriage, during pregnancy, as part of employment requirements, and during routine health screenings [13]. In our study, among the patients included, a total of eight (29.7%) individuals were tested for fever, six (22.2%) for preoperative preparation, three (11.1%) for weight loss, and two (7.4%) for each of the following reasons: job application, diarrhea, prior to blood donation, lymphadenomegaly, and dysphagia.

According to the data from the Ministry of Health, the most common cause of HIV transmission in our country is heterosexual sexual intercourse. Other routes of transmission include sex workers, men who have sex with men, transgender individuals, and intravenous drug use [12]. Similarly, in our study, we observed that the most common route of

transmission among the patients was heterosexual sexual intercourse, which aligns with the national data.

In a study focusing on cancer incidence in individuals living with HIV, it was found that the highest rates of cancer were observed in treatment-naïve individuals, with the lowest rates observed in those on long-term treatment and those who received early treatment [14]. Among individuals living with HIV who are receiving ART, KS and NHL remain common types of cancer [15]. Discontinuation of ART can lead to a decrease in CD4 T lymphocyte levels and the resurgence of HIV replication, thereby increasing the risk of developing lymphoma. Nevertheless, the treatment for lymphoma in HIV-infected patients has become similar to that for the general population [16]. Consistent with findings from other studies, our study also observed NHL in 40.7% of the patients included.

According to available literature, KS is indeed the second most common tumor in individuals living with HIV, especially those with a CD4 count lower than 200 cells/mm³. It has been reported that KS can occur in up to 30% of treatment-naïve HIV patients [17]. Furthermore, the risk of developing KS is observed to increase 5 to 10 times MSM and are living with HIV [17]. In accordance with the literature, our study also determined KS as the second most common tumor among the patients included.

In a study carried out in the United States, it was found that the prevalence of cervical cancer in women with HIV remained 66% higher compared to those without HIV [18]. Notably, the women included in our study exhibited the highest occurrence of cervical cancer.

Some studies have indicated that recurrent bacterial pneumonia poses a risk for the development of lung cancer as it leads to persistent tissue inflammation [19]. This condition is typically diagnosed at a locally advanced or metastatic stage in individuals who are also living with HIV. While smoking has been identified as a major contributing factor to this increased risk, other factors, such as immunosuppression, may also play a significant role, particularly among younger individuals. In individuals aged 50 years and older who have HIV, the incidence of lung cancer surpasses that of both NHL and KS [20]. For our study, the average age of patients diagnosed with lung cancer was 55 years, which aligns with findings from previous studies. Additionally, a

low CD4/CD8 ratio has been associated with a higher incidence of lung cancer, independent of its association with episodes of bacterial pneumonia [8].

In a comprehensive French cohort study on HIV-infected individuals, it was observed that the occurrence of anal cancer was linked to a low CD4 count and prolonged periods of uncontrolled HIV infection [7].

In a study reported high viral load as a risk factor for non-Hodgkin's lymphoma [21]. Another study revealed that individuals with anal cancer who were HIV-positive had an HIV-RNA level of 100,000 copies/ml [22]. In our own study, the highest viral load was detected in cervical cancer cases (466,540 copies/ml), followed by anal carcinoma (247,875 copies/ml).

The CD4/CD8 ratio serves as a reliable indicator of systemic immune activation during ART [23]. Its inverse correlation with the risk of AIDS-related mortality and non-AIDS-defining events, particularly non-AIDS-defining cancers, has been well-established [24]. In an 18-year study involving 83,893 individuals living with HIV, 5,628 of them developed cancer, consistently aligning with a low CD4/CD8 ratio. The most prevalent cancers observed were lung cancer, KS, and NHL [25]. A study conducted in the United States also demonstrated a strong and consistent association between low CD4/CD8 ratio and NHL, lung cancer, and anal cancer, which are the leading causes of cancer-related morbidity and mortality in people living with HIV [6]. In our study, the mean CD4/CD8 ratio corresponded to 0.76, which coincided with findings reported in the existing literature.

CONCLUSION

Although global rates of new HIV infections have decreased in recent years, there has been a significant rise in cases occurring in Eastern Europe, the Middle East, and our own country. Given the positive impact it has on cancer prognosis and treatment outcomes, we think it is crucial to enhance the awareness and knowledge of primary healthcare establishments and oncology healthcare providers regarding AIDS-defining diseases.

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