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Evaluation of Cancers Developed in People Living with HIV: A Single-Center Experience

HIV ile Yaşayan Kişilerde Gelişen Kanserlerin Değerlendirilmesi: Tek Merkez Deneyimi

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ABSTRACT

Introduction: *There is not enough information in the literature about cancer in Turkish human immunodeficiency virus (HIV) patients. This study aims to evaluate the clinical and laboratory profiles of people with HIV/acquired immune deficiency syndrome (AIDS) and malignancy followed in a tertiary hospital in Ankara for 26 years.*

Materials and Methods: *Our study is a retrospective cross-sectional study.*

Results: *In our study, which included 366 patients, the cancer prevalence was found to be 7.1%. Approximately 90% of those in the AIDS-defining cancers (ADCs) group and 37.5% of the non-AIDS-defining cancer (NADCs) group were classified as stage 3, and a significant correlation was found between the Centers for Disease Control and Prevention (CDC) stage at admission and the malignancy group (p= 0.014). The baseline HIV RNA level was higher in the ADCs group (p= 0.043). Similarly, the CD4+ cell count at the time of the diagnosis of malignancy was found to be significantly lower in the ADCs group than in the NADCs group (p= 0.024).*

Conclusion: *Our findings highlight the critical importance of early HIV detection, which facilitates timely initiation of appropriate treatment and cancer screening. This underscores the shared responsibility of not only infectious disease specialists but all divisions of the healthcare system. Our study contributes to increasing awareness in this context.*

Key Words: *Human immunodeficiency virus; Cancer; Turkey; Non-hodgkin lymphoma; Kaposi's sarcoma*

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ÖZ

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Giriş: *Literatürde Türkiye'de yaşayan insan immün yetmezlik virüsü (HIV) hastalarında kanser hakkında yeterli bilgi bulunmamaktadır. Bu çalışmanın amacı, Ankara'da üçüncü basamak bir hastanede 26 yıl boyunca takip edilen HIV/edinsel immün yetmezlik sendromu (AIDS) ve malignitesi olan kişilerin klinik ve laboratuvar profillerini değerlendirmektir.*

Materyal ve Metod: *Çalışma retrospektif kesitsel bir çalışmadır.*

Bulgular: *Çalışma 366 hasta içermekte olup kanser prevalansı %7.1 olarak bulunmuştur. Edinsel immün yetmezlik sendromu tanımlayıcı kanserler (ADCs) grubundakilerin yaklaşık %90'ı ve AIDS tanımlayıcı olmayan kanserler (NADCs) grubundakilerin %37.5'i evre 3 olarak sınıflandırılmıştır ve başvuru sırasındaki Centers for Disease Control and Prevention (CDC) evresi ile malignite grubu arasında anlamlı bir korelasyon bulunmuştur (p= 0.014). Bazal HIV RNA düzeyi ADCs grubunda daha yüksektir (p= 0.043). Benzer şekilde, malignite tanısı sırasında CD4+ hücre sayısı, ADCs grubunda NADCs grubuna göre anlamlı derecede düşük bulunmuştur (p= 0.024).*

Sonuç: *Bulgular HIV infeksiyonunun erken evrede tespit edilmesinin, bireylerin uygun tedaviye erken evrede erişebilmelerinin ve kanser taramasının önemini desteklemektedir. Bu nedenle sadece infeksiyon hastalıkları hekimlerine değil, sağlık sektörünün tüm birimlerine büyük sorumluluk düşmektedir. Çalışma, bu anlamda farkındalığa katkı sağlamaktadır.*

Anahtar Kelimeler: *İnsan immün yetmezlik virüsü; Kanser; Türkiye; Non-hodgkin lenfoma; Kaposi sarkomu*

INTRODUCTION

Human immunodeficiency virus (HIV) has been reported to be a carcinogen by the International Agency for Research on Cancer[1]. In case of infection with HIV, Epstein-Barr virus (EBV) and human herpesvirus-8 (HHV-8) loss caused by oncogenic viruses such as HIV and immune regulation-mediated immune dysfunction as a result of chronic B-cell activation in the induction of chronic antigenic stimulation and the effect of excessive production of cytokines such as HIV lymphomagenesis factors cause is thought to be different. Evidence for direct pro-oncogenic effects of HIV, particularly in lymphomagenesis, has been demonstrated[2].

In addition, oncogenic viruses such as EBV-associated Hodgkin's lymphoma, hepatitis B and C virus-associated liver cancers, and human papillomavirus (HPV)-associated anogenital cancers are implicated in cancer development among people living with HIV[1,3,4]. Low CD4+ cell count is an indicator of immunodeficiency, and the risk of Kaposi's sarcoma (KS) and non-Hodgkin lymphoma (NHL) increases as the CD4+ cell count decreases[5]. In addition, the prevalence of other cancer risk factors (e.g., smoking, excessive alcohol consumption) in the HIV population also plays a role in the etiology[6-9]. KS, NHL, and cervical cancers are common in people living with HIV, and these have been defined as AIDS-defining cancers (ADCs)[10].

In a study conducted in the United States in 2010 among participants living with HIV, 21% had NHL, 12% had KS, 11% had lung cancer, 10% had anal cancer, 7% had prostate cancer, 5% had liver cancer, 5% had colorectal cancer, 4% had Hodgkin's lymphoma, 4% had oral/pharyngeal cancer, 2% had female breast cancer, and 1% had cervical cancer[11]. Additionally, in another study, HIV-infected and HIV-uninfected participants were compared, and the risk of death in cancer patients with AIDS was significantly higher in almost all types of cancer compared to cancer patients without AIDS[12].

The prevalence of cancer in people living with HIV has been reported to be between 2.6 and 5.05%[13,14]. In a study published in 2020, in which 1872 participants living with HIV were followed, mortality was observed at a rate of 22.8% in patients followed up with ADCs and 53.8% in patients followed up with non-AIDS-defining cancers (NADCs), while the death rate was 1.75% in

patients without a diagnosis of cancer[13]. There is limited information in the literature regarding cancer among Turkish HIV patients. This study aims to evaluate the clinical and laboratory profiles of individuals with HIV/AIDS and malignancy who have been followed at a tertiary hospital in Ankara over a 26-year period.

MATERIALS and METHODS

Our clinic is one of the first centers in Türkiye to diagnose and manage HIV/AIDS, having admitted its first HIV/AIDS patient in 1996. Among 366 patients aged 18 years and older living with HIV who were diagnosed and followed between January 1996 and March 2022, 26 patients who were found to have malignancy at diagnosis or during follow-up were included in the study.

The observation period for patients was defined as the time from their first admission to either the date of death, transfer to another institution, or March 31, 2022, whichever came first, for those still under follow-up at the start of the study. Demographic, clinicopathological, and laboratory data of all patients were retrospectively retrieved from patient follow-up records collected for clinical purposes.

The diagnosis of HIV was made by confirming samples with reactive screening with the fourth generation Enzyme-Linked Immunosorbent Assay test by Western blot (HIV BLOT 2.2; MP Biomedicals Asia Pacific, Singapore). CD4+ cell count was measured by standard flow cytometry (FACScalibur; Becton Dickinson, Franklin Lakes, NJ, United States of America), while HIV viral load was measured by polymerase chain reaction (COBAS Ampliprep/COBAS TaqMan HIV-1 Test; Roche Molecular Systems, Pleasanton, CA, USA). Cancer diagnoses were established based on clinical, radiological, and pathological findings.

AIDS-defining disease identification and staging were done according to the Centers for Disease Control and Prevention (CDC) 2014 criteria. According to the CDC classification criteria, KS, NHL, and cervical cancers are classified as ADCs, and all other cancer types are classified as NADCs.

Ethical approval was obtained on March 30, 2022, with the reference number E2-22-1618 from the Scientific Research Evaluation Commission of the Health Sciences University Ankara City Hospital.

Data Analysis and Statistical Evaluation

The suitability of numerical variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were given using frequency tables for categorical variables and median (min-max) for non-normally distributed variables. Pearson's Chi-square and Fisher's exact test were used to compare categorical variables in independent groups, and Student's t-test and the Mann-Whitney U test were used to compare numerical variables in two independent groups. Statistical evaluation was made using SPSS 20.0 software (Armonk, NY). Findings with a p-value less than 0.05 were deemed statistically significant.

RESULTS

Among 366 HIV/AIDS patients followed in our clinic between January 1996 and March 2022, 26 patients diagnosed with cancer were included in the study. Our cancer prevalence was found to be 7.1%.

The median age of the patients at the time of HIV diagnosis was 38 (20-68), and 84.6% (n= 22) were male. Most of them (n= 16, 61.6%) were primary and secondary school graduates. Of the patients, 57.7% (n= 15) had a history of smoking. Intravenous substance use was not reported in any of the patients. Three patients (11.5%) were bisexual, and the remaining 23 patients (88.5%) were heterosexual. Twelve of the patients (46.2%) had comorbid diseases such as hypertension, diabetes, coronary artery disease, hepatitis B, and hepatitis C.

While none of the patients presented with CDC stage 1, approximately 27% were classified as stage 2 and 73% as stage 3 at presentation. The AIDS-defining conditions and opportunistic infections identified at the time of admission are presented in Table 1. Accordingly, AIDS-defining conditions were detected in 73.1% of the participants, while opportunistic infections were identified in 53.8% (n= 14).

The baseline CD4+ cell count was below 200 in 61.5% (16/26) of the patients. At the time of admission, the median baseline CD4+ cell count was 111 (3-519), and the median CD8+ cell count was 658 (91-1908). The CD4/CD8 ratio varied between 0.01-0.90. The median baseline viral load was 113.500 (385-74.3 million).

The longest interval between HIV infection and the diagnosis of malignancy among the patients under follow-up was 14 years. More than half (57.7%, n= 15) were diagnosed with malignancy simultaneously with the diagnosis of HIV infection. Among the 11 patients whose malignancy was not present at the time of HIV diagnosis but developed during follow-up, the median time from HIV diagnosis to malignancy diagnosis was 2.25 years (range= 0.66-14 years). The malignancies identified in the patients are listed in Table 2. Accordingly, 69.2% (n= 18) of the patients were diagnosed with ADCs.

A comparison of clinical features according to ADCs and NADCs groups is shown in Table 3. There was no significant difference between the two groups in terms of gender, median age at the time of HIV diagnosis and malignancy diagnosis, hepatitis B and C co-infection, presence

Table 1. Distribution of AIDS-defining diseases and opportunistic infections detected at the time of admission

	n	%
AIDS-Defining Disease	**19**	**73.1**
Candida esophagitis	8	30.77
Diffuse large B-cell lymphoma	5	19.23
Kaposi's sarcoma	5	19.23
Intestinal cryptosporidiosis	4	15.38
Pulmonary tuberculosis	3	11.54
Pneumocystis jirovecii pneumonia	2	7.69
Opportunistic Infection	**14**	**53.8**
Oropharyngeal/Esophageal candidiasis	7	26.92
Pneumocystis jirovecii pneumonia	3	11.54
Intestinal cryptosporidiosis	3	11.54
Cytomegalovirus retinitis ± esophagitis	2	7.69
Kaposi's sarcoma	2	7.69
Cryptococcal meningitis	1	3.85
Pulmonary tuberculosis	1	3.85
Miliary tuberculosis	1	3.85
Shingles	1	3.85

Table 2. Malignancies detected

	n	%
ADCs*	**18**	**69.2**
Non-Hodgkin lymphoma	9	34.6
Kaposi's sarcoma	8	30.8
Cervical cancer	1	3.8
NADCs†	**8**	**30.8**
Lung cancer	2	7.7
Acute lymphoblastic leukemia	1	3.8
Breast cancer	1	3.8
Penile squamous cancer	1	3.8
Prostate cancer	1	3.8
Endometrial cancer	1	3.8
Ovarian cancer	1	3.8

*ADCs: AIDS-defining cancers, †NADCs: Non-AIDS-defining cancers.

of comorbidities, or smoking. Approximately 90% of those in the ADCs group and 37.5% of the NADCs group were classified as stage 3, and a significant correlation was found between the CDC stage at admission and the malignancy group (p= 0.014). Although the presence of AIDS-defining disease and opportunistic infection at the time of admission was higher in the ADCs group than in the NADCs group, this difference was not statistically significant. The time between HIV infection and the diagnosis of malignancy in the ADCs group was found to be significantly shorter than in the NADCs group (p= 0.043). Cancer was diagnosed simultaneously with HIV in 66.7% of those in the ADCs group, while 37.5% of those in the NADCs group were diagnosed simultaneously. Although ADCs were detected more frequently at the time of HIV diagnosis, NADCs were more frequently diagnosed during follow-up, but this difference was not statistically significant.

Table 3. Clinical characteristics of AIDS-defining cancers and non-AIDS-defining cancers groups

	Overall, n (%) (n= 26)	ADCs, n (%) (n= 18)	NADCs, n (%) (n= 8)	p
CDC phase				
Stage 1	-	-	-	
Stage 2	7 (26.9)	2 (11.1)	5 (62.5)	
Stage 3	19 (73.1)	3 (88.9)	3 (37.5)	0.014
AIDS-defining disease				
Yes	19 (73.1)	15 (83.3)	4 (50.0)	
None	7 (26.9)	3 (16.7)	4 (50.0)	0.149
Opportunistic infection at admission				
Yes	14 (53,8)	12 (66.7)	2 (25.0)	
None	12 (46.2)	6 (33.3)	6 (75.0)	0.090
Diagnosis of malignancy				
Cancer at HIV diagnosis	15 (57.7)	12 (66.7)	3 (37.5)	0.21
Cancer during follow-up	11 (42.3)	6 (33.3)	5 (62.5)	8
Time between HIV-malignancy diagnosis (years), median (min-max)	0 (0–14)	0 (0–12)	0.75 (0–14)	0.043
Patient outcome				
Died	18 (69.2)	14 (77.8)	4 (50.0)	
Alive	8 (30.8)	4 (22.2)	4 (50.0)	0.197

ADCs: AIDS-defining cancers, NADCs: Non-AIDS-defining cancers, CDC: Centers for Disease Control and Prevention.

Table 4. Laboratory parameters of AIDS-defining cancers and non-AIDS-defining cancers groups

	Overall (n= 26)	ADCs (n= 18)	NADCs (n= 8)	p
At HIV diagnosis				
CD4+ cell count <200, n (%)	16 (61.5)	14 (87.5)	2 (12.5)	**0.026**
CD4+ cell count, median (min-max)	111 (3-519)	77 (3-470)	292 (32-519)	**0.023**
HIV-RNA (copies/mL), median (min-max)	113.500 (385-74.300.000)	439.950 (4.196-74.300.000)	60.850 (385-630.000)	**0.043**
During the diagnosis of malignancy				
CD4+ cell count <200, n (%)	18 (69.2)	15 (83.3)	3 (16.7)	**0.022**
CD4+ cell count, median (min-max)	111 (2-585)	71 (2-449)	316 (3-585)	**0.024**
HIV-RNA (copies/mL), median (min-max)	8.540 (0-74.300.000)	479.900 (0-74.300.000)	657 (0-8.540)	**0.004**

ADCs: AIDS-defining cancers, NADCs: Non-AIDS-defining cancers.

The laboratory values at the time of HIV/AIDS diagnosis and malignancy diagnosis in participants with and without ADCs are presented in Table 4. The median baseline CD4+ cell counts were found to be significantly different between the two groups, and the baseline CD4+ cell count was lower in the ADCs group (p= 0.023). Similarly, the percentage of CD4+ cells below 200 was significantly higher in the ADCs group than in the NADCs group (p= 0.026). The baseline HIV RNA level was higher in the ADCs group (p= 0.043). Similarly, the CD4+ cell count at the time of the diagnosis of malignancy was found to be significantly lower in the ADCs group than in the NADCs group (p= 0.024). The percentage of CD4+ cells below 200 and HIV RNA levels were found to be significantly higher in the ADCs group.

Eighteen (69.2%) of the 26 patients with HIV and malignancy died during the follow-up period. Of these patients, eight died from NHL, two from lung cancer, and one from KS, while the others died from non-cancerous causes. Although 77.8% of the participants in the ADCs group and half of those in the NADCs group died, the difference was not statistically significant.

DISCUSSION

A low CD4+ T-cell count, an established marker of advanced immunodeficiency, is strongly associated with an increased risk of both AIDS-defining cancers (ADCs) and non-AIDS-defining cancers (NADCs). In our study, the median CD4+ cell count at the time of cancer diagnosis was 111 cells/μL (range= 2-585). Notably, approximately 70% of the patients had a CD4+ cell count below 200 cells/μL, underscoring the high prevalence of severe immunosuppression at the time of malignancy detection.

In our study, 57.7% of patients received a diagnosis of cancer concurrently with the diagnosis of HIV/AIDS. Notably, the interval between the initial diagnosis of HIV/AIDS and cancer in these cases extended up to 14 years, highlighting the heterogeneity in clinical presentation and detection timing. Among the 11 patients who did not have malignancy at the time of HIV/AIDS diagnosis, the median time from HIV diagnosis to the development of malignancy was 2.25 years (range= 0.66-14 years). These findings underscore the critical importance of vigilant oncological surveillance, particularly at the time of HIV diagnosis and during the early years of follow-up, when the risk of cancer development may be elevated.

The prevalence of cancer in our cohort was 7.1%, which is notably higher than the 2.6% reported in a previous cohort study conducted in Türkiye[13]. This elevated prevalence may be attributed to advanced immunodeficiency resulting from delayed presentation, as well as the referral nature of our institution, a tertiary research hospital managing critically ill patients from across the country. Furthermore, the observation that the majority of our patients had only completed primary or secondary education suggests that limited health literacy and lower socioeconomic status may have contributed to delays in seeking medical care.

The median age of our patients at the time of HIV diagnosis was 38 (20-68), and 84.6% of them were men. In a study by Aydın et al., the mean age was 41.3, and the rate of men was 91.6%[13]. In a study conducted in Korea, the mean age was 42 years, and the rate of men was 88%[14]. In existing literature, most cancers have been reported to be more common in men[15]. Stronger immune responses in women may account for differences in cancer susceptibility between male and female people living with HIV (PLWH)[16]. Our study supports this view.

Homosexual intercourse, intravenous drug use, and hepatitis C virus (HCV) coinfection are frequently reported in many publications[5,8,9,17]. As in our study, heterosexual intercourse and hepatitis B virus (HBV) coinfection were reported more frequently in Aydın et al. and Lee et al.[13,14]. While intravenous drug use was never observed in our study population, it was reported at very low rates in Aydın et al. and Lee et al[13,14]. Sociocultural differences between countries may have played a role in this outcome.

In our study, 57.7% of the participants were current smokers, a rate consistent with findings reported in previous studies[5,17]. Considering

the well-established role of smoking in cancer development-particularly among people living with HIV-the implementation of effective smoking cessation strategies and the provision of appropriate support should be prioritized in the clinical management of these patients[6,8].

In our study, the baseline CD4+ T-cell count was below 200 cells/μL in 61.5% of the patients. This proportion is similar to the findings reported by Aydın et al., whereas studies conducted in Korea, Europe, Asia, and Africa have reported rates of 50%, 48.7%, 72%, and 85.6%, respectively[13,14,18-20]. Given the oncogenic potential of HIV and other coinfecting viruses, prolonged duration of untreated HIV infection increases the risk of cancer development. In our cohort, AIDS-defining illnesses and opportunistic infections were more frequently observed in patients presenting at later stages. Late presentation significantly impacts both cancer and HIV treatment outcomes and may be associated with increased morbidity and mortality.

Similar to other studies, the rate of patients with CD4+ cell counts below 200 at the time of the diagnosis of malignancy was found to be 69.2% (n= 18)[14-17]. In the ADCs group, the CD+4 cell count was lower, and the viral load was significantly higher both at the time of admission and at the time of the diagnosis of malignancy compared to the NADCs group. Since a low CD4+ cell count may be an indicator of delay in diagnosis despite improved diagnostic possibilities, it may be an indication that policies for early diagnosis should be given importance.

In the study group, the median time between HIV infection and the diagnosis of malignancy was 0 (0-14) years. The median time after HIV diagnosis in the Washington cohort was 13.2 years, and the median duration of the DC cohort follow-up was 3.4 years[17]. In our study, similar to the Korean study and Aydın et al., 57.7% of the patients were diagnosed with malignancy and HIV simultaneously[13,14]. In 11 patients whose malignancy was not detected at the time of the diagnosis of HIV infection, the median time from the HIV diagnosis to the diagnosis of malignancy was 2.25 years (0.66-14). Large-scale education about HIV transmission routes, risky behaviors, prevention methods, and early signs can reduce the incidence of disease and malignancy rates while facilitating early diagnosis and treatment. Diagnoses can be made early with cancer screenings in line with the guidelines by providing follow-up for diagnosed participants.

As in Aydın et al.'s Turkish study[13], the Swedish cohort, and the Korean study, most patients were diagnosed with NHL and KS in our study[5,13,14]. Similar to the results of the Korean study, in line with the 2017 general cancer data of the Ministry of Health of Türkiye, lung cancer was the most common NADC in our study, while other cancers were at a similar rate[3,14,21]. In an American study published in 2008, ADCs were detected more frequently than NADCs in participants living with HIV, and the most common cancers were reported as KS and NHL. Lung cancer was found to be the most common NADC[22]. In a study published in 2021, the incidence of NADCs was found to be higher, and the most common NADCs reported were breast cancer and prostate cancer[17]. NADCs and their incidences differ between countries, mainly due to the genetic and socioeconomic characteristics and habits of citizens. Given the frequent association of lung cancer with smoking, smoking cessation policies remain important for participants living with HIV.

In Aydın et al., the mortality rate was reported as 31.25%, and mortality was found to be significantly higher in the NADCs group than in the ADCs group[13]. In the present study, 18 of the 26 patients (69.2%) who were subjected to follow-up with a diagnosis of HIV and malignancy died during the follow-up period. Of these, eight died from NHL, two from lung cancer, and one from KS, while the remainder died from non-cancerous causes. Although 77.8% of participants in the ADCs group and half of those in the NADCs group died, the difference was not statistically significant. A detailed analysis of the high mortality rate in our study revealed that 11 participants (42%) succumbed to cancer-related causes, while seven participants died due

to other comorbidities. The analysis revealed that advanced HIV stage at the time of diagnosis, the diagnosis of cancer in the context of HIV disease, and frequent opportunistic infections, in addition to existing opportunistic infections, were associated with high mortality. Concomitant diabetes, hypertension, and coronary artery disease were also identified as contributing factors. It is therefore vital to consider that early diagnosis of patients will facilitate management.

This study has several limitations. First, the relatively small sample size may limit the generalizability of the findings. Second, the retrospective, hospital-based design relying on medical records introduces potential for information bias. Third, the observational nature of the study precludes conclusions about causality. Finally, due to the limited number of cases for each cancer type, AIDS-defining cancers (ADCs) and non-AIDS-defining cancers (NADCs) were analyzed as separate categories rather than by specific diagnoses.

CONCLUSION

In conclusion, the prevalence of cancer was 7.1%, the most common diagnosis was ADCs, and the most common ADCs were NHL and KS. About two-thirds of our patients died. Most of our patients were diagnosed at CDC stage 3. They were simultaneously diagnosed with HIV infection and cancer. Our findings support the importance of early diagnosis strategies and HIV prevention measures that can be implemented at the national level, as well as the knowledge and awareness of screening and recognizing HIV infection in other specialties. This emphasizes the importance of early detection of HIV infection and access to appropriate treatment and cancer screening for patients in the early stages. Therefore, the responsibility lies not only with infectious disease physicians but with all sectors of the healthcare system. This article is intended to support national-level efforts to raise awareness in this regard.

ETHICS COMMITTEE APPROVAL

This study was approved by the Ankara City Hospital (Decision no: E2-22-1618, Date: 30.03.2022).

CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: HA, BD, AA

Analysis/Interpretation: HA, SK, AA

Data Collection or Processing: HA, SK

Writing: HA, AA

Review and Correction: HA, BD

Final Approval: All of authors

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