Patterns of malignancies in patients with HIV-AIDS: a single institution observational study

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Background With the widespread use of antiretroviral therapy in patients with HIV-AIDS, a prolonged life expectancy is now evident. This has led to an increased incidence of malignancies in this patient population. The spectrum of malignancies in these patients differs worldwide.

Objective To study the patterns of AIDS-defining malignancies (ADMs) and non–AIDS-defining malignancies (NADMs) in patients in India with HIV-AIDS and to analyze the correlation of CD4 counts with the malignancies.

Methods This retrospective study included patients presenting with a malignancy and coexisting HIV-AIDS from January 2013 through December 2016. Patients with CD4 counts at the time of diagnosis of malignancy and having received treatment were analyzed. Analyses of the patient characteristics and correlation of CD4 counts with ADM and NADM were performed.

Results A total of 285 patients were evaluated. The median age was 44.8 years (range, 5-80 years). The mean CD4 count was 235.4 cells/mm^3 (range, 50-734 cells/mm^3; reference range, 500-1,500 cells/mm^3). Cervical cancer was the most common malignancy in women, and non-Hodgkin lymphoma (NHL) was the most common among men. There was a statistically significant difference in CD4 counts between ADMs and NADMs (P = .03). A statistical difference was also noted when the CD4 counts of patients with NHL were compared with other malignancies. However, there was no statistically significant difference noted when CD4 counts of patients with cervical cancer were compared with NADM (P = .914).

Limitations This was a retrospective study and included only patients receiving treatment for malignancies at a single institution.

Conclusions NHL and cervical cancer continue to be the most common malignancies in patients with HIV-AIDS in developing countries. NHL tends to occur in patients with lower CD4 counts.

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India has the third largest HIV epidemic in the world because of its large population size, with 0.3% of the adult population infected with HIV. That translates to 2.1 million infected people, posing a significant challenge in the management of these individuals.[1] In all, 43% of the infected are currently on highly active antiretroviral therapy (HAART).[1] There has been a significant decrease in the number of HIV-AIDS–related deaths in recent years because of the remarkable increase in the use of antiretroviral therapy.[2] However, the prolonged life expectancy in these patients has resulted in an increase in the risk of various new diseases such as cancers. With the complex interactions between altered immunity and infections, the risk of cancers is markedly increased in patients with HIV-AIDS.[3] The spectrum of malignancies in this group of patients differs from that in the general population. In addition, the pattern and the magnitude of malignancies differ in different parts of the world.[4] In this study, we have analyzed the pattern of malignancies in patients with HIV-AIDS in a regional cancer center in India. The aim of the study was to analyze the pattern of malignancies in patients with HIV-AIDS based on their age and sex and to document the CD4 counts at the time the malignancy was diagnosed.

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Methods

We retrieved data from our institution's medical records department on all patients who had HIV-AIDS and had been diagnosed with a malignancy. Data of all patients presenting with a malignancy and coexisting HIV-AIDS from January 2013 through December 2016 were analyzed initially. Only patients for whom there was a documented CD4 count were included in the final retrospective analysis. We analyzed the correlation between the patients' CD4 counts and malignancies subclassified as AIDS-defining malignancies (ADMs; aggressive B-cell non-Hodgkin lymphoma [NHL] and cervical cancer) or non–AIDS-defining malignancies (NADMs; all other malignancies other than aggressive NHL and carcinoma cervix were defined as NADM). We also analyzed the correlation between the CD4 count and NHL and other malignancies. A statistical analysis was performed using SPSS Statistics for Windows, version 23 (IBM Corp, Armonk, NY). The independent sample Mann-Whitney U or Kruskal-Wallis tests were used for comparing the CD4 counts between the various subgroups of malignancies. The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Results

A total of 370 patients who were diagnosed with malignancy and have coexisting HIV-AIDS were identified. In all, 85 patients were excluded because there were no CD4 counts available for them, and the remaining 285 patients were included in the final analysis. Of that total, 136 patients (48%) were men, and 149 (52%) were women.

The median age of the population was 44.8 years (5-80 years) at the time of diagnosis with malignancy. The mean CD4 count of the entire population was 235.4 cells/mm^3 (50-734 cells/mm^3). There were 104 patients with CD4 counts of ≤200 cells/mm^3, and 181 patients had CD4 counts of >200 cells/mm^3 (Table 1). All patients received the HAART regimen, efavirenz-lamuvidine-tenofovir (600 mg/300 mg/300 mg Telura).

The most common malignancies in this population were gynecologic malignancies, followed by hematologic malignancies. Cervical cancer was the most common malignancy among women as well as in the overall study population. Among men, the most common malignancy was NHL. The second and third most common malignancies in men were carcinoma oral cavity and carcinoma oropharynx, respectively, whereas in women, they were NHL and breast cancer. The distribution of various hematologic, head and neck, and gastrointestinal malignancies in this group of patients is shown in Figures 1, 2, and 3.

The ADMs in the study were NHL, including 2 patients diagnosed with primary central nervous system (CNS)

TABLE Patient characteristics and CD4 counts

Diagnosis	No. of patients (N = 285)	Median age, y (range)	Established HIV-AIDS diagnosis[a], n (%)	Mean CD4 count, mm^3	CD4 ≤200 mm^3, n	CD4 >200 mm^3, n
Cervical cancer	80	43.5 (28-80)	52 (65)	239	25	55
Other gynecologic malignancies	8	39 (33-62)	5 (62.5)	306	2	6
Non-Hodgkin lymphoma	59	45 (11-74)	45 (76.27)	195	33	26
Other hematologic malignancies	24	35.5 (5-66)	14 (58.33)	202	10	14
Head and neck cancers	60	45 (22-73)	32 (53.33)	238	23	37
Breast cancer	10	39.5 (36-65)	5 (50)	318	—	10
Gastrointestinal malignancies	24	40.5 (18-68)	14 (58.33)	266	4	20
Genitourinary malignancies	9	45 (36-67)	7 (77.78)	212	5	4
Lung cancers	3	65 (52-71)	2 (66.67)	278	—	3
Other malignancies	8	40.5 (14-72)	6 (75)	307	2	6

[a]Before diagnosis of malignancy.

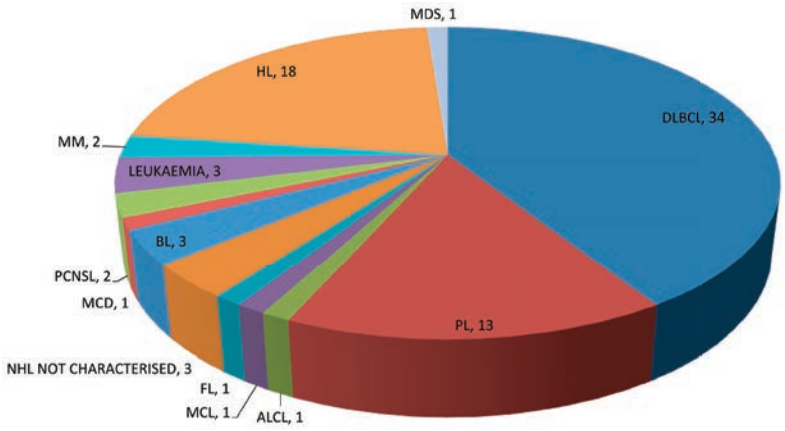

FIGURE 1 Patterns of hematological malignancies.

ALCL, anaplastic large-cell lymphoma; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; MCD, multicentric Castleman disease; MDS, myelodysplastic syndrome; MM, multiple myeloma; PCNSL, primary central nervous system lymphoma; PL, plasmablastic lymphoma

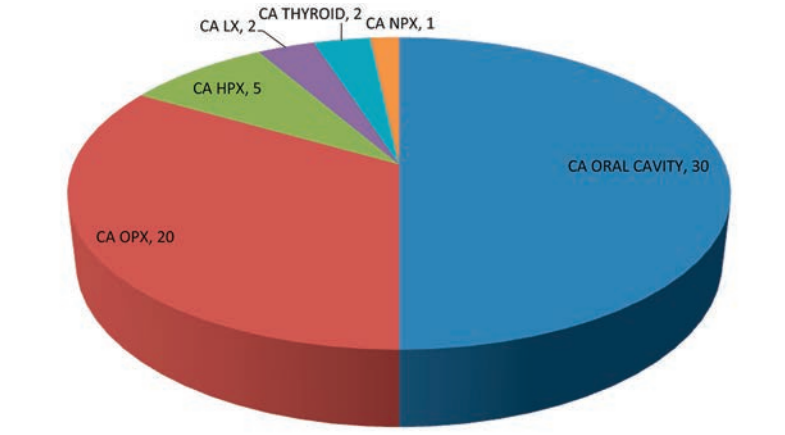

FIGURE 2 Patterns of head and neck malignancies.

CA, carcinoma; HX, hypopharynx; LX, larynx; NPX, nasopharynx; OPX, oropharynx

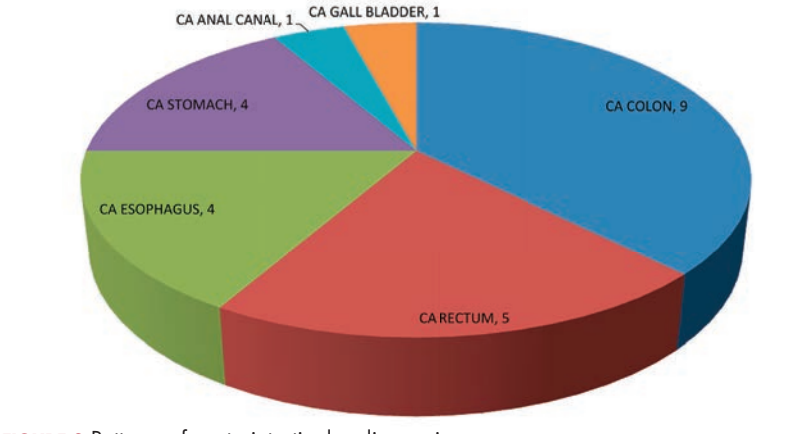

FIGURE 3 Patterns of gastrointestinal malignancies.

CA, carcinoma

lymphomas, and cervical cancer. No case of Kaposi sarcoma, also considered an ADM, was identified in this study. The common NADMs include head and neck malignancies (Figure 2), gastrointestinal malignancies (Figure 3), gynecological and genitourinary malignancies, and breast cancer. The mean CD4 count in the ADM subgroup was 221 cells/mm^3, and in the NADM subgroup, it was 250 cells/mm^3. There was a significant difference in the distribution of CD4 counts between the ADM and NADM subgroups (P = .03; Mann-Whitney U test). A statistical difference was also noted when the CD4 counts of the patients with NHL were compared with other malignancies (P = .0001; Mann-Whitney U test) There was no statistically significant difference noted when CD4 counts of patients with cervical cancer were compared with NADMs (P = .914).

Discussion

In 2015, a report from the Indian government estimated the prevalence of HIV in the country as 0.26% (0.22%-0.32%).[5] The report also noted a decreasing trend in the number of new cases of HIV diagnosed and a decrease in the number of AIDS-related deaths.[5] The decrease in deaths from AIDS is primarily attributed to the widespread use of HAART. With the introduction of HAART therapy, the survival of patients diagnosed with HIV-AIDS has increased markedly.[6] However, newer challenges have emerged with improved survival, such as an increasing number of patients being diagnosed with malignancies. In the current HAART era, the pattern of malignancies in people living with HIV-AIDS has changed compared with the pre-HAART era.[7] The literature suggests that worldwide, malignancies are encountered in about 30% patients with HIV-AIDS, but that percentage differs sharply from that encountered in India, where it is less than 5%.[8] This may partly be explained by opportunistic infections such as tuberculosis in Indian patients, which remains the leading cause of death in the HIV-AIDS population. In our study, we retrospectively analyzed the pattern of malignancies in patients with HIV-AIDS.

Although few studies have quoted NHL as the predominant malignancy in their patients with HIV-AIDS, the predominant malignancy was cervical cancer in our patient population, as seen in few other studies.[8-10] Head and neck malignancies also continue to be common malignancies in men with HIV-AIDS.[10] Thus, an increase in malignancies induced by the human papillomavirus (HPV) can be seen in this group of patients. Only a few

pediatric malignancies were noted in our study, and all of those patients had a vertical transmission of HIV.

Kaposi sarcoma is quite rare in the Indian population, and no case of Kaposi sarcoma was diagnosed in our study population. A similar finding was seen in several earlier publications from India. In the largest published series from India by Dhir and colleagues, evaluating 251 patients with HIV-AIDS and malignancy, no case of Kaposi sarcoma was reported.[10] The authors mentioned that this finding might be because of the low seroprevalence of Kaposi sarcoma-associated herpesvirus in the Asian population.[10] Three different studies from southern India have also not reported the incidence of Kaposi Sarcoma in their series of HIV-AIDS patients with malignancies,[11-13] and similar findings were also reported in a study from northern India.[9] The incidence of other immunodeficiency-related malignancies was identical to those reported in other studies in the literature.[10,14]

As seen in other studies, the CD4 counts in patients with ADM were significantly lower compared with those of patients with NADM, and that difference was not seen when CD4 counts of patients with cervical cancer were compared with patients in the NADM subgroup. The risk of NHL increases proportionally to the degree of immune suppression. The increased susceptibility to various infections in patients with low CD4 counts may also contribute to the occurrence of NHL in patients with low CD4 counts. The occurrence of various other rare cancers in patients with HIV-AIDS may be because of confounding rather than a direct HIV or immunosuppression effect.

An increasing incidence of NADMs has been noted in the Western literature.[7,14] ADMs remain the most common malignancies in the HIV-AIDS population, accounting for about 48% of all malignancies.[8] This is in concordance with previous publications from India.[8,10] With the widespread availability of generic HAART, the incidence of ADMs may decrease even more in the future. In developing countries where the screening procedures for malignancies in both the general population and patients with HIV-AIDS have not yet been implemented at a national level, premalignant lesions of the cervix are not detected.[10] Cervical cancer is the most common malignancy in our study population, which underscores the importance of cervical cancer screening in patients with HIV-AIDS.

In the developed countries, following the introduction of HAART in HIV-AIDS management, the incidence of Kaposi sarcoma decreased by 60% to 70%, and the incidence of NHL decreased by 30% to 50%, whereas the rates of cervical cancer remained either stable or declined.[15,16] Despite the declining trend, the incidence of these malignancies continues to be high among patients with HIV-AIDS compared with the general population.[17] A study from the United States showed increasing trends in various NADMs (such as anal, lung, and liver cancers and Hodgkin lymphoma) from 2006 to 2010.[17] In 2003, the number of patients with NADM were higher than the number of patients with ADM in the United States.[14] In a population-based study from Brazil, ADMs were the most common malignancies diagnosed in patients with HIV-AIDS. A declining trend was noted in the incidence of ADMs in the population and an increasing trend in the incidence of NADMs. This increase in NADM incidence was contributed by anal and lung cancers.[18] Studies from developing countries such as Uganda and Botswana have also shown a decrease in the incidence of Kaposi sarcoma after the introduction of HAART.[19-21]

Kaposi sarcoma, cervical cancer, NHL (including Burkitt lymphoma, immunoblastic lymphoma, and primary CNS lymphoma [PCNSL]) comprise ADMs. All 3 ADMs have an underlying viral infection as the causative agent.[22] Kaposi sarcoma is caused by the Kaposi sarcoma herpes virus, for which seroprevalence varies worldwide.[23] As already noted in this article, the incidence of Kaposi sarcoma among the HIV-AIDS population has decreased worldwide since the introduction of HAART. The preinvasive uterine cervix lesions and carcinoma cervix are caused by HPV. NHL in patients with HIV-AIDS is a predominantly aggressive B-cell neoplasm. Epstein-Barr virus is implicated for most of the ADM NHLs.[24] PCNSL occurs in patients with low CD4 counts and poses a diagnostic challenge. The treatment outcomes for patients with PCNSL before the HAART era were dismal. With the widespread use of HAART, the treatment outcomes of patients with HIV-AIDS and NHL improved, and, currently, these patients are managed the same way as other patients with NHL.[22]

The increasing incidence of the NADM is partly attributed to the increasing incidence of these malignancies in the general population. An elevated risk of certain NADMs is also attributable to viral infections. The common NADMs in the United States are lung, anal, oropharyngeal, and hepatocellular cancers and Hodgkin lymphoma.[14] The common NADMs in our study population were oral, oropharyngeal, colon, and breast cancers and Hodgkin lymphoma. One-third of head and neck cancers, including most oropharyngeal cancers, and cervical and anal cancers in patients with HIV-AIDS are related to HPV.[25] Patients with HIV-AIDS are at increased risk for chronic HPV infection from immunosuppression. Chronic HPV infections and prolonged immunosuppression cause premalignant high-grade squamous intraepithelial lesions and invasive cancers.[22] The initiation of and adherence to HAART leads to immune recovery and reduces high-risk HPV-associated morbidity.[26] Findings from previous studies have demonstrated the benefits of screening for cervical cancer in patients with HIV-AIDS.[27] The HPV vaccine is immunogenic in patients with HIV-AIDS and might help prevent HPV-associated malignancies.[28]

Conclusions

With the wide use of HAART by patients with HIV-AIDS, we can expect an increase in the survival of that population. The incidence of malignancies may also increase significantly in these patients, and further longitudinal studies are needed, as malignancies may emerge as the most common cause of death in patients with HIV-AIDS. In addition, the extensive use of HAART therapy and implementation of screening programs for cervical cancer in patients with HIV-AIDS could result in a decrease in the incidence of ADMs.

References

1. UNAIDS. Prevention gap report. http://www.unaids.org/sites/default/files/media_asset/2016-prevention-gap-report_en.pdf. Released 2016. Accessed December 27, 2017.
2. Department of Health & Family Welfare, Ministry of Health & Family Welfare, Government of India. National AIDS Control Organization (NACO). http://naco.gov.in/sites/default/files/Annual%20Report%202015-16_NACO.pdf. Published July 2016. Accessed December 27, 2017.
3. Dubrow R, Silverberg MJ, Park LS, Crothers K, Justice AC. HIV infection, aging, and immune function: implications for cancer risk and prevention. Curr Opin Oncol. 2012;24(5):506-516.
4. Biggar RJ, Chaturvedi AK, Bhatia K, Mbulaiteye SM. Cancer risk in persons with HIV-AIDS in India: a review and future directions for research. Infect Agent Cancer. 2009;4:4.
5. National AIDS Control Organisation & National Institute of Medical Statistics, ICMR, Ministry of Health & Family Welfare, Government of India. India HIV estimations 2015, technical report. http://www.naco.gov.in/sites/default/files/India%20HIV%20Estimations%202015.pdf. Published 2015. Accessed December 27, 2017.
6. Bonnet F, Lewden C, May T, et al. Malignancy-related causes of death in human immunodeficiency virus-infected patients in the era of highly active antiretroviral therapy. Cancer. 2004;101(2):317-324.
7. Crum-Cianflone N, Hullsiek KH, Marconi V, et al. Trends in the incidence of cancers among HIV-infected persons and the impact of antiretroviral therapy: a 20-year cohort study. AIDS. 2009;23(1):41-50.
8. Sharma S, Soneja M, Ranjan S. Malignancies in human immunodeficiency virus infected patients in India: initial experience in the HAART era. Indian J Med Res. 2015;142(5):563-567.
9. Sachdeva RK, Sharma A, Singh S, Varma S. Spectrum of AIDS defining & non-AIDS defining malignancies in north India. Indian J Med Res. 2016;143(suppl 1):S129-S135.
10. Dhir AA, Sawant S, Dikshit RP, et al. Spectrum of HIV-AIDS related cancers in India. Cancer Causes Control. 2007;19(2):147-153.
11. Venkatesh KK, Saghayam S, Devaleenal B, et al. Spectrum of malignancies among HIV-infected patients in South India. Indian J Cancer. 2012;49(1):176-180.
12. Shruti P, Narayanan G, Puthuveettil J, Jayasree K, Vijayalakshmi K. Spectrum of HIV/AIDS-associated cancers in south India. J Clin Oncol. 2014;32(suppl):e12534.
13. Paul TR, Uppin MS, Uppin SG, et al. Spectrum of malignancies in human immunodeficiency virus–positive patients at a Tertiary Care Centre in South India. Indian J Cancer. 2014;51(4):459-463.
14. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst. 2011;103(9):753-762.
15. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. Ann Intern Med. 2008;148(10):728-736.
16. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer. 2008;123(1):187-194.
17. Robbins HA, Shiels MS, Pfeiffer RM, Engels EA. Epidemiologic contributions to recent cancer trends among HIV-infected people in the United States. AIDS. 2014;28(6):881-890.
18. Tanaka LF, Latorre MDRD, Gutierrez EB, Heumann C, Herbinger KH, Froeschl G. Trends in the incidence of AIDS-defining and non-AIDS-defining cancers in people living with AIDS: a population-based study from São Paulo, Brazil. Int J STD AIDS. 2017;28(12):1190-1198.
19. Mutyaba I, Phipps W, Krantz EM, et al. A population-level evaluation of the effect of antiretroviral therapy on cancer incidence in Kyadondo County, Uganda, 1999–2008. J Acquir Immune Defic Syndr. 2015;69(4):481-486.
20. Dryden-Peterson S, Medhin H, Kebabonye-Pusoentsi M, et al. Cancer incidence following expansion of HIV treatment in Botswana. PLoS ONE. 2015;10(8):e0135602.
21. Shiels MS, Engels EA. Evolving epidemiology of HIV-associated malignancies. Curr Opin HIV AIDS. 2017;12(1):6-11.
22. Yarchoan R, Uldrick TS. HIV-associated cancers and related diseases. N Engl J Med. 2018;378(11):1029-1041.
23. Gao SJ, Kingsley L, Li M, et al. KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma. Nat Med. 1996;2(8):925-928.
24. Epstein-Barr virus and AIDS-associated lymphomas. Lancet. 1991;338(8773):979-981.
25. Picard A, Badoual C, Hourseau M, et al. Human papilloma virus prevalence in HIV patients with head and neck squamous cell carcinoma. AIDS. 2016;30(8):1257-1266.
26. Minkoff H, Zhong Y, Burk RD, et al. Influence of adherent and effective antiretroviral therapy use on human papillomavirus infection and squamous intraepithelial lesions in human immunodeficiency virus-positive women. J Infect Dis. 2010;201(5):681-690.
27. Ghebre RG, Grover S, Xu MJ, Chuang LT, Simonds H. Cervical cancer control in HIV-infected women: past, present and future. Gynecol Oncol Rep. 2017;21:101-108.
28. Kojic EM, Rana AI, Cu-Uvin S. Human papillomavirus vaccination in HIV-infected women: need for increased coverage. Expert Rev Vaccines. 2016;15(1):105-117.