

## Original article

# Patterns of neoplastic diseases among HIV-infected and HIV-uninfected patients

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**Abstract:** In order to investigate the association between the human immunodeficiency virus (HIV) type-1 and neoplasms, we analyzed the pattern and rates of neoplastic disorders among HIV-positive and HIV-negative patients. A total of 108 incident neoplastic diseases were diagnosed among 4272 subjects tested for HIV at Tikur Anbessa Teaching Hospital, Addis Ababa, from September 1994 to March 1997. Forty-eight (1.1%) incident tumors were diagnosed among 2701 patients seropositive for antibodies to HIV-1 and 60 (1.4%) among 1573 seronegatives. There was no statistical difference on the occurrence of tumor in the HIV-positive or HIV-negative subjects (Odds ratio=0.48; 95% confidence interval=0.32,0.72). Kaposi's sarcoma (KS) was the most frequent neoplastic disease among HIV-positive subjects (47.9%) and it was strongly associated with HIV seropositivity (Odds ratio=13.5; 95% confidence interval=1.95, 268.99). Non-Hodgkin's lymphoma (NHL) (22.9%) and Hodgkin's disease (HD) (18.8%) were the other frequent neoplasms. Most (73%) of the HIV-related NHL were of the high grade type; 64% of these tumors were extranodal and 55.6% of all NHL occurring in HIV-negative subjects were of the high grade type; only 33.3% were extranodal. NHL of the low grade type was less frequent in HIV-positive subjects compared to HIV-negative subjects (9.1 vs. 25.9%; Odds ratio= 4.08; 95% confidence interval 0.51, 88.42). Significant cases of cervical carcinomas (37.5%), classified histologically as squamous cell carcinomas, were associated with HIV infection, although it was not statistically significant (Odds ratio=0.44; 95% confidence interval=0.08, 2.29). In the HIV-uninfected subjects, NHL was the most common neoplasm (45%) followed by HD (15%), hematological malignancies (10.1%) and cervical carcinomas (8.3%). Data from the present study demonstrate that some neoplasms are frequently associated with the current trends of the HIV/AIDS epidemic in Ethiopia. Many new AIDS-related neoplasms will likely continue to be identified in the future. [*Ethiop. J. Health Dev.* 1998;12(2):117-123]

## Introduction

Neoplastic diseases are being reported with increasing frequency in patients infected with the human immunodeficiency virus type-1 (HIV-1) (1-6). In particular, neoplasms such as Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) have been clearly associated with HIV infection. Furthermore, a wide spectrum of tumors occur with increased frequency in patients with the acquired immunodeficiency syndrome (AIDS), though they have not yet been included as an AIDS-defining diseases. In the developed countries, more than 40% of AIDS patients develop neoplastic disorders some time during the course of their disease (4,5). However, there is little information regarding the pattern and incidence of neoplastic diseases in HIV infected subjects

in Ethiopia. In a previous report (7) from Ethiopia, Shamebo M. showed that NHL was significantly associated with HIV infection. Another recent report (8) also showed that KS is being diagnosed increasingly during the last five years in the Department of Pathology of the Tikur Anbessa Teaching Hospital (TATH). This led the authors to propose that the HIV/AIDS epidemic in the country might be responsible for the observed increased incidence of the tumor. This study was, therefore, undertaken in order to determine the pattern and rates of neoplastic diseases that may

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be associated with HIV-1 infection and to compare results with uninfected subjects so as to see the impact of the HIV/AIDS epidemic on the pattern of occurrence of neoplastic disorders.

**Methods**

A total of 4274 HIV serology tests were performed between September 1994 and March 1997 at the AIDS laboratory of the TATH. During the same period 103 patients with a diagnoses of neoplastic diseases were tested for HIV serology. The medical records of these patients were reviewed. The following informations were collected: patient's age, sex, biopsy reports and clinical characteristics. All biopsy slides were reevaluated by one of the authors (W.E.) for reconfirmation. The diagnoses of neoplasms were based on morphological features of biopsy sections. Slides were stained with hematoxylin and eosin (9). Only histologically proved neoplasms were included for this study. Hematological malignancies were diagnosed on peripheral and bone marrow smears stained with Wright's stain. NHL were classified according to the criteria described in the Working Formulation of the Non-Hodgkin's lymphoma Pathologic Classification System (10). HD were classified according to the Rye Histological Classification system (11). Antibodies to HIV-1 were determined by an ELISA assay (vironostika HIV Uni-Form II, Organon teknika, Netherlands) according to the manufacturer's manual. Patients were excluded if information from the medical records were incomplete (n=9), or if the biopsy findings were not reconfirmed (n=5) or if the diagnosis were non-neoplastic diseases (n=7).

The patterns of neoplastic diseases were analysed and compared with the results of the serological tests for HIV-1 with use of the EPI-Info version 6.0 software package. X<sup>2</sup> analyses and Fischer's exact tests were used to compare associations. P values less than 0.05 were considered as significant.

**Results**

During the study period, a total of 4274 HIV serology tests were performed at the AIDS Laboratory of the TATH. Of these, 2701 (63.2%) were seropositive for antibodies to HIV-1 and the remaining 1573 (36.8%) were negative. During the same period there were 103 subjects (2.4%) diagnosed with neoplastic disorders out of which 48 (1.1%) incident tumors occurred in 47 HIVpositive subjects and 60 (1.4%) in 56 seronegatives. There was a statistical difference on the occurrence of tumor in the HIV-positive or HIV-negative subjects (Odds ratio=0.48; 95% confidence interval=0.32,0.72). These 103 were 72 males and 31 females, (male:female ratio 2.3:1) with age ranges of between 18 and 78 years. The mean age was 36.7 years. The mean age in the HIV-positive patients was 35.5 years compared to 37.8 years in the seronegative patients.

Table 1: Age distribution of neoplasms in HIV-negative HIV-positive patients.

| Age group HIV | HIV      |          |
|---------------|----------|----------|
|               | negative | positive |
| 15-19         | 9(16.1)* | 0(0.0)   |
| 20-20         | 8(14.1)  | 11(23.4) |
| 30-39         | 14(25.0) | 20(42.5) |
| 40-49         | 11(19.6) | 14(29.8) |
| 50-59         | 9(16.1)  | 2(4.3)   |
| ≥60           | 5(8.9)   | 0(0.0)   |
| Total         | 56       | 47       |
|               | 9(16.1)* | 0(0.0)   |

\*Numbers in parentheses are percentages.

As shown in Table 1, the peak age of neoplasm was between 30-39 years. However, the frequency was higher in the HIV-positive subjects than in HIV-negative subjects (42.5% vs. 25%). The histological classification of the neoplasms is summarized in Table 2. The most frequent type of neoplastic disease in the HIV-positive subjects was KS (47.9%). One patient with KS had also cervical carcinoma. Furthermore, KS was strongly associated with HIV seropositivity (Odds ratio=13.5; 95% confidence interval=1.95, 268.99). The only patient with KS who were seronegative for HIV was a 73 year old man. The most

Table 2: **Patterns and frequency of incident<sup>1</sup> neoplasms in HIV-negative and HIV-positive patients.**

| Morphological classification | HIVnegative | HIV-positive | Odds ratio (95% CI) | P-value                |
|------------------------------|-------------|--------------|---------------------|------------------------|
| Kaposi'sarcoma               | 1           | 23           | 13.50(1.95, 268.99) | P<0.01                 |
| Non-Hodgkin's lymphoma       |             |              |                     |                        |
| High grade lymphoma          | 15          | 8            | 0.31(0.12, 0.77)    | NS                     |
| Intermediate lymphoma        | 5           | 2            | 0.23(0.03, 1.34)    | NS                     |
| Low grade lymphoma           | 7           | 1            | 4.08(0.51, 88.42)   | P<0.05                 |
| Hodgkin's lymphoma           |             |              |                     |                        |
| Lymphocyte predominant       | 1           | 2            | 1.16(0.08, 32.43)   | NS                     |
| Mixed cellularity            | 5           | 5            | 0.58(0.15, 2.31)    | NS                     |
| Nodular sclerosing           | 3           | 1            | 0.19(0.01, 2.07)    | NS                     |
| Lymphocyte depleted          | -           | 1            | NA                  |                        |
| Hematological malignancies   |             |              |                     |                        |
| Chronic lymphocytic leukemia | 4           | --           | NA                  |                        |
| Plasmacytoma                 | 1           | --           | NA                  |                        |
| Multiple myeloma             | -           | 1            | NA                  |                        |
| Cervix carcinomas            |             |              |                     |                        |
| Squamous cell carcinoma      | 4           | 3            | 0.44(0.08, 2.29)    |                        |
| Adenocarcinoma               | 1           | --           | NA                  |                        |
| Oronasopharyngeal carcinomas | 3           | --           | NA                  |                        |
| Breast cancers               | 2           | --           | NA                  |                        |
| Miscellaneous <sup>2</sup>   | 7           | 1            | 0.08(0.00, 0.66)    |                        |
| Total                        | 60          | 48           | 0.48(0.32, 0.72)    | significant difference |

Includes<sup>1</sup> the occurrence of more than one type of neoplasm in a patient.

Include<sup>2</sup> such tumors like Wilm's tumor, hemangiosarcomas, skin cancers (other than KS) and neurofibrosarcomas.

Abbreviations: CI; confidence interval; NA: not applicable; NS; not significant

frequent presentation of the tumor was a disseminated skin lesions (n=12). Other sites involved include skin of the lower extremities (n=10), oral (n=1) and lymph node (n=1). The second common type of tumor in the HIV-positive patients was NHL (22.9%) followed by HD (18.8%). Among the HIV-negative group, however, NHL (45%) was the most common type of tumor followed by HD (15%), hematological malignancies (10.1%) and cervical carcinomas (8.3%), in descending frequency.

Among the 11 cases of HIV-related NHL, most (73%) were of the high grade type. Of all HIV-related NHL, 64% were extranodal: five in the gastrointestinal tract, one in the lung and one in the perianal region. On the other hand, of the 27 cases of NHL occurring in HIV-negative subjects, 55.6% were of the high grade type and only 33.3% were extranodal [five in gastrointestinal tract; two in lung, two in breast and one in liver]. NHL of the low grade type was less frequent in HIV-positive subjects compared to HIV-negative subjects (9.1% vs. 25.9%; Odds ratio=4.08; 95% confidence interval 0.51, 88.42). The disease was advanced (stage IIB and IVB) in 73% of the patients with HIV infection compared to only 33% of HIV uninfected persons. Most (56%) of the nine cases of HIV-associated HD were of mixed cellularity sub-type. Furthermore, the disease was advanced with stages IIB and IVB presentations in 56% of the cases as compared to 33% among HIV-negative subjects.

In addition to the known AIDS-related neoplasms, subjects who were seropositive for HIV had cervical carcinomas. Although statistically not significant (Odds ratio= 0.44; 95% confidence interval=0.08,2.29), a large proportion of cervical carcinomas (37.5%), were associated with HIV infection. These HIV-related cervical carcinomas were all undifferentiated, invasive squamous cell carcinomas. In general, HIV uninfected subjects had more often other solid tumors. None of the patients with oronasopharyngeal tumors were HIV infected.

## Discussion

Individuals with AIDS are at risk of developing not only opportunistic infections, but also a wide spectrum of neoplastic disorders. The latter in particular is attributed to the improved management of patients with HIV infection, namely, appropriate treatment and prophylaxis of opportunistic infections coupled with antiretroviral chemotherapy (2,4,5).

The mean age of our patients with neoplastic disorders, irrespective of their HIV status, coincides with that of HIV patients in the general population (12). However, those with neoplastic disorders and who were HIV-positive present at younger age than HIV seronegative persons because 65.9% of the HIV-positive patients were younger than 40 years compared to only 55.2% HIV-negative patients. Although there is no significant difference on the rate of neoplasms between HIV-positive and HIV-negative patients, the pattern in the AIDS subjects is comparable to that seen in other countries (1-6). The reason for a lower rate of malignancy among the HIV-positive subjects might be the fact that physicians request HIV tests only when they diagnose the commonly known AIDS-related neoplasms. Moreover, the life expectancy among Ethiopian AIDS patients is too short for a neoplastic disease to appear and the majority of the patients die from associated opportunistic infections (12).

KS was considered a rare tumor previously (13,14) and during the early AIDS epidemic (15) in Ethiopia. The present study, however, showed that KS is the most frequent neoplasm identified among the HIV-positive subjects. This is in agreement with a more recent report (8) which showed a trend towards a significantly increased incidence of the tumor during the last five years. Until November 1994, a total of 40 (0.3%) cases of KS has been diagnosed among 15565 AIDS cases reported in the country (16). The present study, however, demonstrated that 23 (0.9%) cases were detected among 2701 AIDS patients seen only over thirty months of the study period. The results indicate that there is a significant increase in the incidence of the tumor. This might be due to the increased awareness of physicians with a high index of suspicion. Likewise, an increase in the incidence of KS has been described in other African countries since the onset of the AIDS epidemic (17,18). Patients with the epidemic form of KS (i.e. HIV-related) are younger, and the male:female

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ratio (4.6:1) is much lower than in endemic forms of KS (18). This is in agreement with our present study where the male:female ratio was 4.8:1. The epidemic form of KS has a much more fulminant clinical presentation. The disseminated form of KS was noted in 52.2% of the HIV-positive patients. The pathogenesis of KS in AIDS is not known definitely yet. Opportunistic infections have also been associated with the *de novo* appearance of KS in AIDS patients (19). High circulating levels of inflammatory cytokines which have been demonstrated in the face of opportunistic infections may account for these effects on KS (19). Other possible factors suggested include profound HIV-induced immunosuppression, chronic antigenic stimulation, and a sexually transmitted agent (19).

Lymphoproliferative disorder incidence among HIV-positive patients as reported previously (7) was 22.2% for NHL and 9.1% for HD. Our study showed a significant increase to 28.9 % (11/38) and 50% (9/18) for NHL and HD, respectively. NHL of the low-grade type was more frequent among HIV-negatives patients as previously reported (7). However, NHL of the high grade type was more frequent among HIV-negatives, although the association was not statistically significant. The findings confirm the conclusion of prior studies (1-7) that these neoplasms are additional manifestations of AIDS. Although AIDS patients have significantly greater risk of developing NHL, it is also a much more common neoplasm than KS in the general population. Histologically, the types of NHL related to AIDS are most commonly of the high grade type, but intermediate grade NHL might also be seen among AIDS subjects (20). Extranodal sites of NHL were frequent in our AIDS cases as is also reported previously (1,3,7). Although primary central nervous system (CNS) lymphomas are frequently reported in AIDS patients (20), it is rarely recognized in Ethiopia. The reason might be due to the low rate of biopsy specimens taken from the CNS as it is also known that most AIDS patients with intracranial space occupying lesions are treated frequently for possible opportunistic infections as a whole.

There is accumulating evidence linking AIDS with HD in homosexual men (21). Although not yet accepted as a diagnostic criteria for AIDS, HD may occur with increased frequency in HIV-positive subjects as is also seen in the present study. HD and AIDS are both relatively common in young persons, a substantial number of HD cases in AIDS patients can be expected to occur by coincidence alone rather than true association. As is also shown in Table 1, in the age group 15-19 years, there were 9 HIV-negative patients diagnosed with tumors as compared to none among HIV-positive subjects. The reason for this is that, in our series of patients, about 44.4% of all HD cases in HIV-negative patients occurred in the above age group, whereas about 55.6% of all cases of HD in HIV-positive patients occurred in the age group 40-49 years. Nevertheless, HD presents with advanced stage with histologically mixed cellularity sub-type in most of the patients with AIDS.

Cervical cancer has recently been recognized as an AIDS defining disease in patients infected with HIV (22). The present study showed that 37.5% (3/8) of all subjects with cervical cancer were HIV infected. Only the invasive, histologically undifferentiated squamous cell carcinomas were associated with HIV infection. Cervical cancer is the leading type of malignancy seen in women in most of the developing world including Ethiopia (14, 23, 24). Epidemiologically cervical cancer is strongly associated with lifestyles leading to increased risk of sexually transmissible infectious agents in addition to HIV (25). A lack of effective cancer screening and treatment programs (24) in the face of high rate of sexually transmitted infections are among the reasons for the observed high incidence of cervical cancers in these countries. Hence we should anticipate to see more cases of cervical cancer occurring among women of the child bearing age group in the face of the growing AIDS epidemic in these countries. Women with newly diagnosed cervical carcinomas, particularly those with advanced disease, should be counseled and offered HIV testing.

The rate of detection of other solid tumors among HIV-positive subjects was small. Although multiple myeloma was reported to occur among AIDS patients (26) and as has also occurred in one of our AIDS patients, these probably represent a coincidental occurrence rather than a true association with HIV infection. None of the three patients with oronasopharyngeal malignancies were associated with HIV infection. A recent report from Sudan (27) agrees with our observation. There is, however, a paucity of one type of neoplasm in particular, namely hepatocellular carcinoma, that one might surmise would be seen in excess among HIV positive populations. Nevertheless, the emergence of this tumor as a significant neoplastic complication of AIDS has not been demonstrated, as is also suggested by others (28,29).

Because of the small number of the cases, the results from the present study should be interpreted with caution. However, this study has demonstrated an increase in the incidence of KS, NHL and HD that is consistent with trends in the magnitude of the HIV/AIDS epidemic in Ethiopia (12). Furthermore, the findings confirm that, besides opportunistic infections, neoplasms are other important manifestations of AIDS in the country. The data presented here demonstrate the need for the awareness of clinicians of neoplastic disorders that are not well recognized as AIDS-related neoplasms. With the improved management of opportunistic infections in AIDS patients and increased survival, many new malignancies will likely continue to be identified. The study underscores the need for well designed prospective studies in the future to determine the impact of HIV epidemic on the incidence and pattern of neoplastic disorders in the country.

#### **Acknowledgements**

We thank Professor Jakob Schneider, Department of Pathology, Faculty of Medicine, Addis Ababa University, and Dr. Yemane Berhane, Department of Community Health, Faculty of Medicine, Addis Ababa University, for their critical review of the manuscript and useful suggestions.

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