Original Article

HIV-associated lymphomas: A clinicopathological study from India

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ABSTRACT

Background: Although there is a high burden of HIV-positive cases in India, there is very little published data on the prevalence and pathological profile of malignancies occurring in these patients. **Aims:** The current study was undertaken to analyze the clinicopathological profile of HIV-positive patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). **Materials and Methods:** This was a retrospective study over a 6-year period consisting of histopathology slide and clinical chart review of HIV-positive patients with lymphomas. **Results:** Of a total of 3470 HIV-positive patients during the 6-year period of study, the number of HIV patients diagnosed with lymphomas was 26. The mean duration between HIV seropositivity and development of lymphoma was 12 months. Seven patients were diagnosed as HIV positive during the course of investigations after a lymphoma diagnosis. The male to female ratio was 5.5:1 and the mean CD4 count, 171/mm^3. Among the 26 cases, 3 were diagnosed with classical HL and the rest with NHL. B-cell lymphomas predominated with 19 cases. Among the NHLs, plasmablastic lymphoma and diffuse large B-cell lymphoma were the common subtypes with no cases of either Burkitt Lymphoma or primary CNS lymphoma. The median duration of follow-up was 1 year. Ten cases died during the course of treatment, 11 cases achieved complete remission. **Conclusions:** This is one of the few studies from India documenting the clinicopathological features of HIV-associated lymphomas. It is interesting that in many cases, HIV positivity was detected during the course of investigations after a lymphoma diagnosis.

Key words: HIV, lymphomas, plasmablastic lymphoma

INTRODUCTION

India has a huge burden of HIV-positive individuals despite the steady decline in prevalence from 0.41% in 2000 through 0.36% in 2006 to 0.31% in 2009. According to the National AIDS Control Organisation estimates, there are approximately 2.4 million HIV patients in India. It is believed that there are more seropositive cases in India than any other country in the world.[1] Despite the large number of cases, there is very little published data regarding the types of malignancies occurring in these patients. While certain high-grade non-Hodgkin lymphomas (NHLs), invasive cervical carcinoma, and Kaposi sarcoma are considered AIDS-defining, other malignancies occurring in these patients are considered non-AIDS defining.

Patients with HIV are at increased risk of developing both Hodgkin lymphoma (HL) and NHL. HIV patients are more likely to develop high-grade NHLs and also extranodal lymphomas. The higher occurrence of high-grade lymphomas among HIV patients was first reported in 1984.[2] With the advent of highly active antiretroviral (HAART) therapy, the outcomes of these patients have improved considerably in the west. Today, patients who receive a combination of antiretroviral and lymphoma-directed therapies achieve outcomes comparable to those of HIV-negative patients.[3]

Although HIV-associated lymphomas are an important concern in India, there are limited studies regarding

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the clinicopathological profiles of HIV patients with lymphomas. Therefore, we undertook this study of lymphomas occurring in HIV patients presenting to our institution, a tertiary care center. The emphasis was mainly on the histological subtypes and clinical profiles.

MATERIALS AND METHODS

We retrospectively reviewed the records of HIV patients diagnosed with lymphomas both HL and NHL between the 6-year period 2008–2013. Demographic data, clinical staging of the lymphomas, CD4 counts at the time of diagnosis, treatment history, outcomes, and any other relevant data were retrieved from the case charts. The histopathology and immunohistochemistry (IHC) data were reviewed by us.

The diagnosis of HIV was established by ELISA testing and confirmed with Western blot in these cases. The CD4 counts were performed by the flow cytometric method. Lymphoma staging was done by Ann Arbor protocol. Imaging studies, bone marrow examination, and serum lactate dehydrogenase levels were done for staging. Paraffin embedding with routine hematoxylin and eosin staining were performed for routine morphology. IHC was done on paraffin-embedded tissue sections which were 3–4 microns thick. Antibodies were obtained from commercial sources and included a panel of relevant markers. Standard DAB detection method with polymer technology was used in the protocol. All the variables were entered on Microsoft excel, and the means were calculated using the same.

RESULTS

A total of 3470 HIV-positive patients were registered in our institution before starting antiretroviral therapy during the 6-year period between 2008 and 2013. The total number of HIV patients diagnosed with lymphomas was only 26 (0.74%). The mean duration between HIV seropositivity and development of lymphoma was 12 months. Seven patients were diagnosed as HIV positive during the course of investigations after a lymphoma diagnosis. The demographic data and clinical stages are summarized in Table 1. With 22 males and 4 females, the male to female ratio was 5.5:1. The CD4 count ranged from 4 to 503/mm^3 with a mean count of 171/mm^3.

Among the 26 cases, 3 were diagnosed with classical HL and the rest with NHL [Table 2]. B-cell lymphomas predominated with 19 cases, whereas 4 cases were left unclassified as IHC was not performed on these cases. Ten cases were nodal lymphomas, and the rest were extranodal. The extranodal sites involved are summarized in Table 3, gastrointestinal tract (GIT) being the most common extranodal site [Figure 1].

Table 1: Clinical features of HIV patients with lymphomas

???	???
Number of cases	26
Age (years): Range	10-58
Median	39.5
Sex	
Male	22
Female	4
Male:female ratio	5.5:1
Median duration from HIV positivity to diagnosis of lymphomas (months)	12
Number of patients diagnosed to have HIV infection during workup for lymphoma	7
CD4 count	
Mean CD4 count at the time of diagnosis (/mm^3)	171
Range (/mm^3)	4-503
Stage III/IV (%)	15 (58)

Table 2: Histological subtypes of lymphomas

Subtypes of lymphomas	Number of patients (*n*=26) (%)
Classical HL	3 (11.5)
NHL	23 (88.5)
B-cell	19 (82.6)
PBL	8 (42)
DLBCL	7 (37)
MALT	2 (11)
FL Grade II	1 (5)
Unclassified	1 (5)
NHL unclassified	4 (17.4)

PBL: Plasmablastic lymphoma, DLBCL: Diffuse large B-cell lymphoma, MALT: Mucosa-associated lymphoid tissue, FL: Follicular lymphoma, NHL: Non-Hodgkin's lymphoma, HL: Hodgkin's lymphoma

Table 3: Sites of involvement: nodal and extranodal

Site of involvement	Number of patients (%)
Nodal	
Cervical, axillary, mediastinal, mesenteric	10 (38)
Retroperitoneal and inguinal lymph nodes	16 (62)
Extranodal	4
Head and neck (hard palate, maxillary sinus, gingiva, oral cavity)	1
Respiratory tract (lower trachea, bronchus, vocal cord)	8
Gastrointestinal tract (stomach, duodenum, ileum, jejunum, colon, and anal canal)	
Kidney	1
Ovary	1
Prostate	1

Diffuse large B-cell lymphoma (DLBCL) and plasmablastic lymphomas (PBLs) were common subtypes seen in seven and eight patients, respectively. While DLBCL showed typical morphology with large cells which were CD20 positive [Figure 2a and b]. PBL showed large cells with prominent nucleoli and it was positive for CD138 [Figure 3a and b].

Treatment history and outcomes are shown in Table 4. The median duration of follow-up was 1 year. Ten cases died during the course of treatment, 11 cases achieved complete

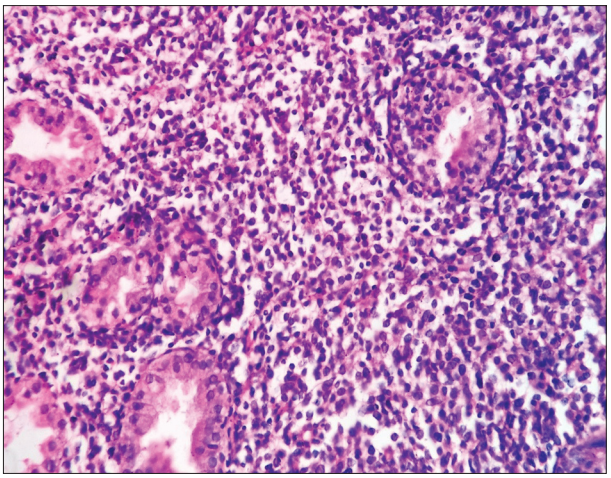

Figure 1: Mucosa-associated lymphoid tissue lymphoma, stomach (H and E, ×20)

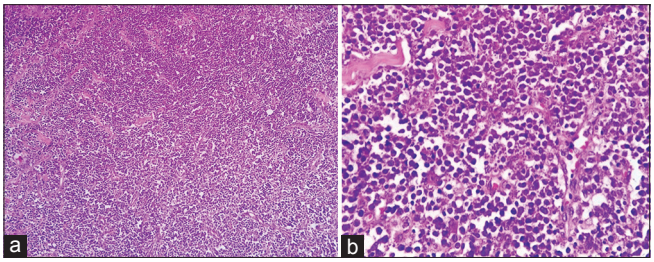

Figure 2: (a) Diffuse large B-cell lymphoma, lymph node (H and E, ×4), (b) Diffuse large B-cell lymphoma, lymph node (H and E, ×10)

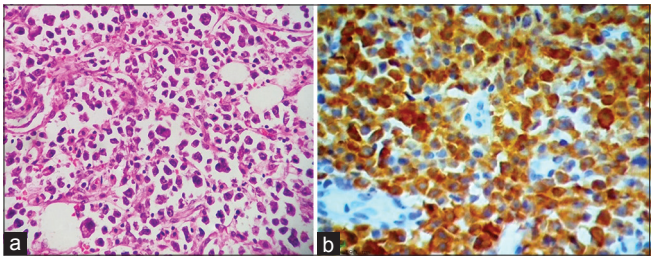

Figure 3: (a) Plasmablastic lymphoma, oral cavity (H and E, ×40) (b) Plasmablastic lymphoma, oral cavity (CD138, ×40)

remission. Associated opportunistic infections and other events are highlighted in Table 5. Fifty-eight percent of the patients presented at Ann Arbor Stage III/IV.

As shown in Table 5, tuberculosis was a commonly associated infection in this study with 3 cases, one of which showed disseminated disease.

DISCUSSION

India has a huge burden of HIV-positive cases.[4] Table 6 shows a comparison of the current study with other published studies from India. However, there are very few studies from India that highlight prevalence and types of lymphomas that occur in patients with HIV infection. Some are just limited to small case series.[5] In a large study of 135

Table 4: Treatment, response, and follow-up

	Number of patients
Treatment received (*n*=18)	
R-CHOP	11
CVP	1
CEOP	1
VTD	1
ABVD	3
REPOCH	1
Patients on treatment with antiretroviral therapy	18
Response and follow-up (*n*=21)	
Complete remission	11
Death during the course of treatment	10 (within 6-160 days)
Relapse	2
Median duration of follow-up (year)	1

Table 5: Other associated infections/events

Other associated infections/events	Number of patients
Oral candidiasis	2
Pulmonary tuberculosis	2
Disseminated tuberculosis	1
Hepatitis B surface antigen positive	2
Renal failure	3
Malignant pleural effusion	3
Lymphomatous meningitis	1

hospitalized HIV-infected patients from North India, only 2 cases of lymphomas were found, infections being the most common cause for hospitalization.[6] In the current study, out of 3740 patients enrolled for HIV treatment, only 26 cases were found to have lymphomas (0.74%).

In the current study, a male to female ratio of 5.5:1 was seen with only 4 females out of a total of 26 patients. All the previous studies have found a male preponderance as seen in the current study. Sirsath *et al.*'s study of 18 cases had a male to female ratio of 1.6:1.[7] Dhir *et al*. found a male to female ratio of 3:1.[8] The male preponderance seen in all the studies may be a reflection of higher prevalence of HIV positivity in males as a whole.

The median ages of patients in previous Indian studies are 38 years and 39.5 years.[7,8] This is in concordance with the current study of 39.5 years. Some western studies have reported a slightly higher median age (44 years) for HIV-associated lymphomas.[9]

The largest study from Mumbai, which studied 277 cases of NHL in HIV-infected patients, found that DLBCL was the most common subtype being 42.9% of all NHL.[10] Burkitt lymphoma constituted 12.5% of all NHLs in that study. In the current study, DLBCL accounted for 37% of all NHLs, whereas there were no cases of Burkitt lymphomas. PBL, which occurs more commonly in patients with HIV

Table 6: Comparison with other Indian studies on HIV-associated lymphomas

Factors	Current study	Dhir *et al.*[3] (TMH, Mumbai)	Sirsath *et al.*[4] (KIDWAI, Bengaluru)	Sharma *et al.*[5] (AIMS, New Delhi)
Period of study	2008-2013	2001-2007	2008-2012	2003-2007
Number of cases	26	277	18	7
Median age (years)	39.5 (10-58)	38	39.5 (27-62)	- (14-56)
Male:female ratio	5.5:1	3:1	1.6:1	2.5:1
Male	22	208	11	5
Female	4	69	7	2
Stage III/IV (%)	58	53.6	66.7	86
Mean CD4 count	171/mm^3	-	218/mm^3	243/mm^3
	4-503/mm^3	<200/mm^3 to 67.9%	38-316/mm^3	18-454/mm^3
Site of involvement (%)				
Nodal	10 (38)	111 (40)	10 (55.5)	3 (43)
Extranodal	16 (62)	166 (60)	8 (44.5)	4 (57)
Histological subtypes (%)				
HL	11.5	-	27.8	-
NHL	88.5	100	72.2	100
B-cell (%)	82.6			
DLBCL	37	42.9	50	43
PBL	42	25	11.1	14
FL	5	-	-	14
Burkitt's (%)	-	12.5	-	-
MALToma (%)	11	-	-	-
Primary CNS lymphoma	-	-	11.1	-
Unclassified	5	-	-	-
T-cell	-	-	-	-
Unclassified (%)	17.4	18.5	-	29

PBL: Plasmablastic lymphoma, DLBCL: Diffuse large B-cell lymphoma, MALToma: Mucosa-associated lymphoid tissue lymphoma, FL: Follicular lymphoma, CNS: Central nervous system, NHL: Non-Hodgkin lymphoma, HL: Hodgkin lymphoma

infection, was the most common subtype in the current study accounting for 42% of all NHLs. In the study by Sirsath *et al*., 5 of 18 (28%) patients had HL and the rest NHL.[7] In our study, there were three patients with HL, all of which were nodal. In a study by Venkatesh *et al*. who analyzed all cancers occurring in HIV-infected patients in South India, the most common type of cancer in HIV-infected patients was NHL (38.1%) followed by HL (16.7%).[11] High-grade lymphomas occur more commonly in HIV patients when compared to the general population, and this is reflected in all the Indian studies including the present study.[6]

Interestingly, there were no cases of primary CNS lymphoma (PCNSL) in this study. This could be attributed to a referral bias, wherein these cases may be presenting to hospitals and institutions primarily catering to neurological illnesses. Further, a large multicentric hospital-based study did not reveal any increase in the incidence of PCNSL in HIV/AIDS patients in India over a 24-year period.[12]

Sixty-two percent of our cases were extranodal, GIT being the most common location for extranodal disease [Figure 1]. This finding is in concordance with the study by Srisath *et al*.[7]

CD4 count is one of the indices used for monitoring response to HAART therapy in patients with HIV/AIDS. It is well known that the risk of developing NHL is inversely related to the CD4 counts.[13] While PCNSLs develop in patients with very low CD4 counts, the other subtypes such as DLBCL and Burkitt Lymphomas occur in patients with higher CD4 counts. In the current study, the mean CD4 count was 171/mm^3 with a range of 4–503/mm^3. This value is comparable to the other studies, namely, <200/mm^3, 218/mm^3, and 243/mm^3.[8,14] The median duration of HIV diagnosis to diagnosis of lymphoma was 12 months in the current study. In the study by Sirsath *et al*., this duration was 18 months.[7] It is interesting to note that in this study, seven patients were detected to be HIV positive during the course of investigations after the diagnosis of lymphoma. In the study by Sirsath *et al*., 26 out of a total of 44 patients were diagnosed to have HIV infection during the workup for lymphoma.[7] This shows that there may be a large number of undetected HIV patients in the Indian population who are tested HIV positive during the workup for malignancy.

Follow-up was available in 21 patients, of which ten (48%) died during the course of treatment. We were able to obtain follow-up in the majority of our patients, which was a strength of this study. In one of the previous Indian studies, follow-up was obtained in only 9 out of 26 patients.[7] Treatment of NHL is challenging in these patients as they are already immunodeficient and chemotherapy results in exacerbation of cytopenias. Treatment also increases the risk of opportunistic infections. Tuberculosis remains the most common opportunistic infection in Indian patients with HIV.[15] Associated mycobacterial infection was also noted in 3 of our patients.

CONCLUSIONS

Although India carries a huge burden of HIV, there is limited literature regarding the malignancies occurring in these patients, lymphoproliferative disorders in particular. Some are just limited to small case series.[5] This study was an attempt to study the various subtypes and clinical profiles of HIV patients with lymphomas in our setup. In many cases, HIV positivity was diagnosed during the course of investigations after a lymphoma diagnosis. Increased awareness and further studies are warranted to improve outcomes in these patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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