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Original Article

Hematologic derangements in HIV/AIDS patients and their relationship with the CD4 counts: a cross-sectional study

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Abstract: Objective: Hematologic abnormalities are the most common complications of human immunodeficiency virus (HIV) infection being more pronounced during the late stages of the disease, thereby indicating the progressive nature of the disease. Anemia is the most frequent hematologic abnormality in HIV. However, leukopenia, lymphopenia, and thrombocytopenia have also been observed. We undertook this study to evaluate the hematologic abnormalities in HIV patients and their relationship with the CD4 cell counts. Materials and methods: This is an analytical cross-sectional study that was carried out among patients in Jammu, India for the three years from 2015 to 2018. Data collection pro-forma has two parts. Firstly, socio-demographic details such as age, gender, marital status, and occupation were noted. Secondly, investigations such as HIV testing, complete blood counts and CD4 counts were considered. The Statistical Package for Social Sciences (SPSS) software version 20 was used for data entry and analysis. One way analysis of variance (ANOVA) was applied as appropriate to examine differences between quantitative variables. Results: Anaemia was present in 72.5% of cases in our study. Leukopenia, lymphopenia and thrombocytopenia were observed in 18.33%, 49.17%, and 15.83% of the cases, respectively. We found statistically significant relationships of anemia, absolute lymphocyte count, and thrombocytopenia with the CD4 counts ($P<0.0001$, $=0.018$ and $=0.044$, respectively). However, CD4 counts at the time of presentation were not significantly related to the total leukocyte count and absolute neutrophil count. Conclusions: Anemia was the most frequent hematologic abnormality in HIV patients followed by lymphopenia, leukopenia, and thrombocytopenia. A significant relationship was observed between the anemia, absolute lymphocyte count, and thrombocytopenia with the CD4 counts. We recommend routine hematologic investigations and timely treatment for all the hematologic derangements in HIV patients.

Keywords: Hematologic abnormality, HIV, AIDS, anemia, CD4 counts

Introduction

Human Immunodeficiency virus (HIV) infection is characterized by progressive weakening of the immune system attributed to the decrease in the number of circulating $CD4^+$ T-helper cells. This predisposes HIV patients to a variety of opportunistic infections and neoplastic disorders. The most severe phase of HIV infection leads to Acquired Immunodeficiency syndrome (AIDS) where the $CD4^+$ cell count drops below 200/mm^3. It is marked by the appearance of particular opportunistic infections [1].

HIV infection leads to a multisystem disease with prevailing hematological abnormalities. Hematological aberrancies become more severe during the late stages of the disease signifying the importance of active virus replication and high levels of viremia in the causation of disease [2, 3]. They include defective haematopoiesis, cytopenias affecting various cell lineages, and abnormalities of coagulation. These abnormalities are due to diverse reasons which include immune-mediated destruction of cells, direct cytopathic effects of the virus, secondary to various infections and neoplasms, and drug toxicity [4]. The most prevalent haematological

disorder observed in children and adults with HIV infection is anemia. Incidences of anemia are particularly high in patients with late stages of the disease and a reduced CD4 cell count. Anemia has been linked with the advancement of the disease and increase in mortality [5-7].

Leukopenia is also a common occurrence, especially in patients with advanced stages of the disease [8-10]. Neutropenia has been observed in all stages of the disease. Lymphopenia primarily involves CD4 T-helper cells and is considered the classic hallmark of the disease. Lymphopenia worsens with the progression of the disease [11]. HIV-infected patients frequently present with dysplastic changes in neutrophils which includes bizarre nuclei, high N:C ratio, hypogranularity, and nuclear fragmentation [12]. Thrombocytopenia is found in all the stages of HIV; the prevalence being highest in the late stages of disease and with low CD4 cell counts [13-16]. Myelodysplastic changes have been observed in a large number of HIV patients and these changes can be detected in all the stages of the disease. Most common infectious agents involving the bone marrow in patients with AIDS are mycobacteriosis, histoplasmosis, and toxoplasmosis [17, 18].

This study is an analytical cross-sectional study to assess the hematological abnormalities in HIV/AIDS patients and to correlate these abnormalities with the CD4 cell counts.

Methodology

The present study is an analytical cross-sectional study and was implemented on the patients registered at Dr. Bhardwaj's Diagnostic Laboratory, Jammu, India. A retrospective data of three years from March, 2015 to February, 2018 was retrieved from the files of the patients. Dr. Bhardwaj's Diagnostic Laboratory received blood samples for various hematological investigations from HIV-positive patients registered at the Voluntary Counselling and Testing Centre (VCTC), Government Medical College Hospital, Jammu. Exclusion criteria of the study include: suffering from malignancy not related to HIV/AIDS, pregnancy, and <16 years of age. The total number of patients validated for the study was 120. The research was conducted after ethical approval from Jammu and Kashmir State AIDS Control Society (Approval no: JKSACS/Adm/19/171). The de-identified data were collected from files of patients. Hence, the ethical committee of Jammu and Kashmir State AIDS Control Society exempted the authors from the necessity to obtain informed consent.

Data collection pro-forma has two parts. Firstly, socio-demographic details such as age, gender, marital status, and occupation were noted and secondly, investigations such as HIV testing, complete blood counts, CD4 counts were recorded. Case was defined as AIDS if it met criteria as specified by the National AIDS control society (NACO, 2007) [19].

Investigations

1. HIV detection tests: Comb Test (COMBAIDS for detecting HIV1 & 2) and ELISA Tests (GENEDIA HIV 1/2 RAPID 3.0 kits) were employed for diagnosing HIV infection.

2. Complete haematological evaluation was done first at the time of presentation. Blood collection and processing was done as per guidelines of National AIDS Control Organisation (NACO, India). The haematological investigations comprised of: a) Complete Blood Counts (CBC) by automated cell counter. This included the haemoglobin estimation, total erythrocyte count, total leukocyte count, differential leukocyte count, and platelet count; b) Peripheral blood examination after staining the blood film by Romanowsky stains; and c) Erythrocyte sedimentation rate (ESR) measurement was done by Westergren's method [20].

3. CD4 cell counts: BD FACSCOUNT flow cytometer (Becton Dickenson and Company, California, USA) was used for CD4 cell counts.

4. Other routine investigations included routine urine examination, renal function tests, liver function tests, and chest X-rays. All patients were screened for associated sexually transmitted diseases (STD), i.e., for HCV, HBsAg, and VDRL.

5. Investigations like bone marrow aspiration/marrow trephine biopsy, USG abdomen, Mantoux test, and sputum for AFB were done as and when needed.

HIV patients were categorized into three clinical categories: Category A, B, and C based on the

Table 1. Socio-demographic and disease characteristics (n=120)

Variable		n (%)
Age group (in years)	≤40	87 (72.5)
	>40	33 (27.5)
Gender	Male	69 (57.5)
	Female	51 (42.5)
Marital status	Unmarried	3 (2.5)
	Married	108 (90)
	Divorced/Widow	9 (7.5)
Mode of transmission	Sexual	105 (87.5)
	Blood	5 (4.17)
	Unknown	10 (8.33)
On regular HAART		97 (80.83)
Presence of HBV/HCV Co-infection		17 (14.17)

Data are presented as frequencies; n and (%).

Table 2. Hematological abnormalities in HIV infected patients (n=120)

Variable	n (%)
Leukopenia	22 (18.33)
Lymphopenia	59 (49.17)
Neutropenia	6 (5.0)
Anemia	83 (69.17)
Thrombocytopenia	19 (15.83)

revised CDC classification system (1993). The three $CD4^+$ T-lymphocyte categories are as follows: Category 1: greater than or equal to 500 cells/μL; Category 2: 200-499 cells/μL; and Category 3: less than 200 cells/μL [21].

Data analysis

The Statistical Package for Social Sciences (SPSS) software version 20 was used for data entry and analysis. Descriptive statistics were presented as frequency (numbers; n), percentage and mean ± SD. *P* values <0.05 was considered as statistically significant. Analysis of Variance (ANOVA) was used to examine differences between quantitative variables.

Results

In our study, male preponderance (57.5%) was observed. Male: female ratio was 1.35:1. Majority of the patients (72.5%) were in the age group ≤40 years. We found that 90% of the patients were married, 7.5% divorced or widowed and only 2.5% were unmarried. Sexual mode of transmission was the predominant mode of spread in our study and was found in 87.5% cases. 90 patients (80.83%) were on regular HAART treatment while HBV/HCV coinfection was found in 17 (14.17%) of cases (**Table 1**).

Anemia presented in 87 cases (72.5%). Leukopenia was observed in 22 patients (18.33%) and lymphopenia in 59 cases (49.17%). We found thrombocytopenia in 15.83% of the cases while neutropenia was observed only in 5% of the cases (**Table 2**).

In terms of the clinical categories, 47 patients were in the category A (4 patients in A1, 35 in A2, and 8 patients in A3); 43 patients in category B (4 patients in B1, 26 in B2, and 13 patients in B3); and 30 patients in category C (3 patients in C1, 4 in C2, and 23 patients in C3). With regard to CD4 counts, only 11 patients from all clinical categories had CD4 counts >500/μL, 65 patients had CD4 counts between 200-499/μL, and 44 patients had CD4 counts <200/μL (**Table 3**).

Hb levels and RBC counts were statistically significant when associated with CD4 counts (P<0.0001 and = 0.009, respectively). However, statistical–significance was not observed with the TLC and ANC parameters. We observed lymphopenia in 59 cases (49.17%) and a statistical significant relation was found between ALC and CD4 counts (P=0.018). We observed thrombocytopenia in 19 cases (15.83%) and it was significantly related to CD4 counts (P=0.044) (**Table 4**).

Discussion

Hematological abnormalities are quite commonly observed in all the stages of HIV infection. In view of the resource constraints in developing countries like India, measurement of the hematological parameters assumes paramount importance. These measurements can be used as prognostic markers predicting the progression of the disease. We undertook this study to evaluate the haematological derangements in HIV patients and to correlate these derangements with the CD4 counts. Our study showed a predominance of males (57.5%), with male: female ratio of 1.35:1. Male predominance was observed by Dikshit et al., De Santis et al., and Parinithia and Kulkarni in 67.5%, 68%, and 61.6% of their cases, respectively [2, 22, 23]. Majority of our patients (72.5%) aged

Table 3. Clinical categories (CDC 1993 Revised classification system) of the HIV patients

$CD4^+$ T-cell categories	Clinical categories			Total
	A (Asymptomatic)	B (symptomatic)	C (AIDS indicator conditions)	
>500/μL	04 (A1)	04 (B1)	03 (C1)	11
200-499/μL	35 (A2)	26 (B2)	04 (C2)	65
<200/μL	08 (A3)	13 (B3)	23 (C3)	44

Data shown are n.

Table 4. Relationship of haematological parameters with CD4 counts of the HIV patients

CD4 count (cells/μL)	<200 (n=44)		200-499 (n=65)		≥500/μL (n=11)		P
Hb (g/dL)	9.23	±1.21	10.82	±1.84	11.77	±1.58	<0.001*
RBC count ($\times 10^6/mm^3$)	3.69	±0.41	3.91	±0.39	4.02	±0.54	0.009*
TLC ($/mm^3$)	6850.59	±2133.71	7078.95	±2355.67	7180.91	±1281.64	0.835
Neutrophils (%)	64.69	±7.01	62.93	±6.47	59.29	±8.13	0.059
Lymphocytes (%)	30.27	±6.12	32.75	±6.96	36.12	±8.13	0.024*
Monocytes (%)	2.18	±0.54	2.17	±0.34	2.05	±0.42	0.657
Eosinophils (%)	2.86	±0.78	2.53	±0.95	2.54	±0.87	0.150
ANC cells/μL	4350.12	±1385.35	4658.59	±1890.03	4489.97	±1685.12	0.649
ALC cells/μL	1823.38	±559.01	2036.98	±531.35	2332.23	±778.6	0.018*
Platelets ($\times 10^3/\mu L$)	189.23	±32.3	208.31	±45.1	213.82	±49.2	0.048*

*Statistically significant (P<0.05). Data shown are mean ± SD and *P* value.

≤40 years. In the study of Enawgaw et al. [16], it was found that 90% of their patients were <45 years old, whereas DeSantis et al. [22] found a mean age <42 years. In our study, the majority of the patients were married (90%). Enawgaw et al. found that 14.5% of the patients were single, whereas the other patients were married, widow or divorced. We found that sexual mode of transmission was the most common (87.5%). De Santis et al. found sexual transmission in 73.7% of cases [22]. Dikshit et al. found unprotected heterosexual exposure in 93.5% of their cases [2].

Hematologic abnormalities have been found to be strong prognosticators of morbidity and mortality in HIV patients [24]. Hematological abnormalities are mostly observed in the category 2 and 3 HIV patients but anemia and thrombocytopenia have been reported even in the early stage of HIV infection [25]. One of the most frequently occurring hematologic complications in HIV patients is the development of anemia, which is associated with decreased survival, increased disease progression, and deterioration in the quality of life. Factors contributing towards the development of anemia in HIV patients include sex and race of the patient, low CD4 counts, anti-HIV medications, and high viral load [26]. Opportunistic infections and myelosuppression by drugs also plays a dominant role in the pathogenesis of anemia [5, 27]. Anemia being the most common haematological abnormality in HIV patients is more prevalent in advanced stages of the disease [28]. The prevalence of anemia varies widely ranging from as low as 22.2% to as high as 90.9% in the studies done in different population groups [29, 30]. Anaemia was present in 72.5% cases in our study. Prevalence of anemia was found to be higher in the various studies done in India, as has been reported by Panwar et al. [31] in 86.4% of cases, Tripathi et al. [17] in 90% of cases, and Pandey A et al. [32] in 74.7% of the cases. Dikshit et al. found anemia in 65.5% of their patients [2]. The most common type of anemia observed in our study was normocytic normochromic anemia accounting for about 42.34% of cases (**Figure 1**). Panwar et al. found normocytic normochromic anemia in 46% of cases [31]. Kasthuri et al. [33] and Tripathi et al. [17] also reported "normocytic normochromic" as the most common type of anemia in HIV patients.

Leukopenia in AIDS patients has been attributed to defective granulopoiesis, infections, malignancies, and anti-granulocyte antibodies

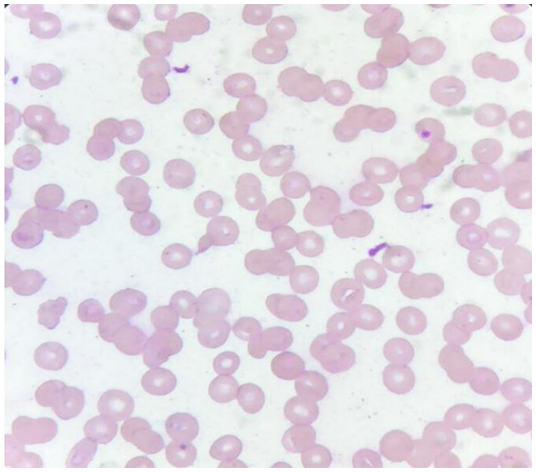

Figure 1. Peripheral blood smear shows the presence of normocytic normochromic anemia in a HIV patient (Leishman stain 100×).

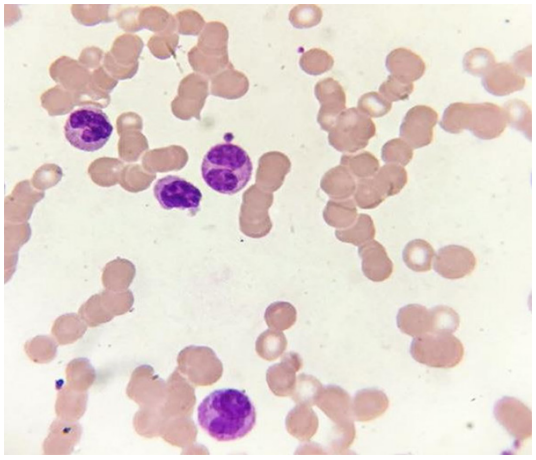

Figure 2. Peripheral blood smear showing presence of hypolobulated neutrophils and a bilobed neutrophil in a HIV patient (Leishman stain 100×).

[34]. Toxicity of the drugs used to treat HIV infection also plays an important role in the pathogenesis of leukopenia [35]. The pathogenetic factors which account for neutropenia encompass direct cytopathic effects, myelodysplasia, drug toxicity, infections, and malignancies (**Figure 2**). Lymphopenia, especially involving CD4 T-helper cells, is predominantly due to the direct cytopathic effects of the virus [11]. In our study, leukopenia was observed in 18.33% patients and lymphopenia in 49.17% of the cases. Similar observations were made by Tripathi et al., Parinitha and Kulkarni, Thulasi et al., and Treacy et al. [17, 23, 35, 36].

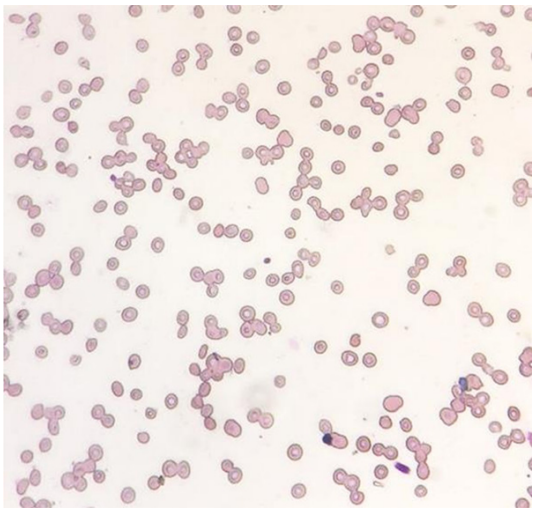

Figure 3. Peripheral blood smear shows the decrease in the number of platelets (thrombocytopenia) in a HIV patient (Leishman stain 100×).

The prevalence of thrombocytopenia in HIV patients ranges from 3.74-40% in different studies (**Figure 3**). Different mechanisms responsible for thrombocytopenia include the immune mediated and non-immune mediated mechanisms [37, 38]. We found thrombocytopenia in 15.83% of the cases. Many other studies have found thrombocytopenia in the range of 13 to 18% such as those conducted by Parinitha and Kulkarni [23], Patwardhan et al. [39], and Costello C [40].

In our study, severe anemia was observed in the HIV patients with lowered CD4 counts in contrast to the patients having higher CD4 counts. The RBC parameters, like Hb and RBC counts, were significantly related to CD4 counts ($P<0.0001$ and $P=0.009$ respectively). Parinitha and Kulkarni also found that the number of cases of anemia increased with decreasing CD4 counts and it was statistically significant [23]. Dikshit B et al. [2], De Santis et al. [22], Thulasi et al. [35], and Vanker et al. [41] found an increased incidence of anemia with decreasing CD4 counts.

We did not observe a significant relationship when CD4 counts were correlated with the total leukocyte count and absolute neutrophil count. Devi CS et al. observed lower TLC and ANC counts with decreasing CD4 cell counts, but did not find significant correlations between them [42]. Dikshit et al. did not find any cases of neutropenia in their study conducted on 200 HIV

patients. Moreover, they did not find a significant relationship between CD4 counts and the total leucocyte count [2]. However, Parinitha and Kulkarni found significant correlations of CD4 count with total leukocyte count where lowered CD4 counts lead to lowered total leucocyte counts [23]. Vanker et al. found a statistically significant relationship between declining $CD4^+$ counts and TLC and neutrophil counts [41].

In our study, lymphopenia was observed in 49.17% of the cases. The relationship between the absolute lymphocyte count and CD4 counts was statistically significant (P=0.018). Parinitha and Kulkarni found a significant relation between CD4 count and each of lymphopenia and absolute lymphocyte counts [23].

Thrombocytopenia was observed in 15.83% of the cases in our study and the relationship with the CD4 count was statistically significant (P=0.044). Enawgaw et al. found a significant increase in thrombocytopenia cases with decrease in CD4 counts (P=0.007). De Santis et al. [22] and Katemba et al. [43] also found a significant association between decreasing $CD4^+$ cell counts and thrombocytopenia. However, some of the authors failed to find a significant relationship between thrombocytopenia and CD4 counts [35, 41]. Dikshit et al. [2] and Parinitha and Kulkarni [23] found thrombocytopenia in 7% and 18% of their patients, respectively but did not find a significant relation with CD4 counts.

Conclusions

Derangements in the hematological profile are frequent in HIV patients. The most frequent hematological abnormality is anemia followed by lymphopenia, leukopenia and thrombocytopenia. A statistically significant relationship was noted between the anemia and the declining CD4 counts. Absolute lymphocyte count and thrombocytopenia also showed a significant association with CD4 counts thereby implying the adverse effect of lowered CD4 counts on the disease progression. We recommend routine haematological investigations as reliable and cheap prognostic indicators in HIV patients and appropriate treatment for all the haematological derangements.

Disclosure of conflict of interest

None.

Abbreviations

HIV, Human immunodeficiency virus; AIDS, Acquired immunodeficiency syndrome; CBC, Complete blood counts; ESR, Erythrocyte sedimentation rate; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HAART, Highly active antiretroviral therapy; RBC, Red blood cell; TLC, Total leucocyte count; ANC, Absolute neutrophils count; ALC, Absolute lymphocyte count.

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