



Haematological changes in HIV infection with correlation to CD4 cell count

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RESEARCH

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Abstract

Background

HIV infection is associated with a wide range of haematological abnormalities.

Methods and Objectives

The objectives in this study were to study haematological changes in HIV patients and to correlate them with CD4 cell counts. Two hundred and fifty HIV positive patients referred to the haematology laboratory section for complete haemogram in whom CD4 count was done were included in the study. Haematologic parameters and CD4 counts were studied in each of these patients.

Descriptive statistics were applied. Association between two attributes was calculated by chi-square test and p value less than 0.05 was considered statistically significant.

Results

Among 250 patients, anaemia was seen in 210 (84%) cases. The most common type was normocytic normochromic (40.4%). Lymphopenia was seen in 163 (65.2%) cases and thrombocytopenia in 45 (18%) cases. The majority of cases (70%) had CD4 cell counts below 200 cells/mm³. Fifty-four cases (21.6%) had CD4 counts between 200 to 499 cells/mm³ and 21 (8.4%) cases had CD4 counts more than 500 cells/mm³.

In patients with CD4 counts less than 200 cells/mm³, anaemia was seen in 91.4% cases, leucopenia in 26.8%

cases, lymphopenia in 80% cases and thrombocytopenia in 21.7% cases.

Conclusion

Haematologic manifestations of HIV infection are common and more frequent with progression of disease. The present study revealed a significant increase in the number of cases of anaemia, and lymphopenia, with decreasing CD4 cell counts. Thrombocytopenia is also seen but does not show significant increase with disease progression. The study also highlights the importance of simultaneously treating HIV patients for haematologic manifestations to reduce morbidity.

Key Words

HIV, CD4 count, Peripheral blood smear, Total leucocyte count, haematological

What this study adds:

1. This study highlights the various haematological changes occurring in HIV infection which can itself be the cause of morbidity.
2. Total lymphocyte count can be used as predictor of CD4 cell count in developing countries where CD4 cell estimation may not be possible.
3. Along with HIV infection and secondary infection haematological problems should also be treated.

Background

Acquired immunodeficiency syndrome (AIDS) was first recognised in 1981 and human immunodeficiency virus (HIV) was identified in 1983.¹ Globally the phenomenon of HIV/AIDS is best viewed as a pandemic affecting nearly all the countries of the world.² In India there were an estimated 22.7 lakh individuals living with HIV/AIDS by the end of 2008 with an adult prevalence of 0.29%.³

Disorders of the haematopoietic system including anaemia, leucopenia and thrombocytopenia are common throughout the course of HIV infection. These could be due to direct effects of HIV infection, secondary infections, neoplasms or side effects of therapy.¹ There are few studies on haematological changes in HIV and very few have correlated



results with CD4 count. In the present study haematologic changes have been correlated with CD4 cell counts to highlight these manifestations with disease progression.

Method

The present study was performed between November 2004 and May 2006 in the department of pathology. HIV seropositive patients were referred from various departments to the haematology section for complete haemogram, those in whom CD4 count was done were included in the study. Patients on antiretroviral therapy (ART) and those in whom a complete haemogram was not done were excluded from the study. Ethical clearance from the institutional ethical committee was obtained.

Haematology parameters were analysed in haematology auto analyser Sysmex KX-21 which analyses using three detector blocks. White blood cell (WBC) count, red blood cell (RBC) count and platelets are measured using direct current detection method. The blood sample fed into the analyser enters the transducer chamber having minute aperture on both sides of which are electrodes between which flows direct current. As blood cells pass through aperture there is change in electrical resistance and blood cell size is detected as electric pulses. Blood cell count is calculated by counting the pulses and a histogram is plotted which is analysed to obtain various analysis data. Differential leucocyte count was done on peripheral smear stained with leishmann stain. Erythrocyte sedimentation rate (ESR) was done by Westergren method. CD4 lymphocyte count was done in BD FACS Calibur flowcytometer, an automated multicolour system that performs both analysis and sorting using dual lasers 488nm air cooled argon-ion laser and 635nm red diode laser. Cells are treated with monoclonal antibodies CD3, CD4 and CD45 conjugated to different fluorochromes. As a cell passes through the flow chamber, it is intersected by a laser beam. Forward light scatter is proportional to the cell size and right angle scatter is related to cell granularity which allows separation of WBCs based on size and granularity. Analysis of fluorescent signals helps in delineating subpopulations. Data was analysed by cell quest software.

Statistical tests used included mean, standard deviation, ANOVA (analysis of variance), chi-square test (χ^2). The data was entered in a Microsoft Office 98 Excel worksheet and statistical analysis was done using SPSS version 12. Descriptive statistics were applied; p value less than 0.05 was considered statistically significant.

Results

During the study period 482 HIV patients were referred to the haematology laboratory. One hundred and sixty two patients were on ART and in 70 patients the request from the clinician was only for haemoglobin and blood counts. These patients were excluded from the study. Two hundred and fifty patients were included in the study, the age ranged from 4 years to 65 years. Mean age was 34.55 ± 9.63 years. Nine (3.6%) patients were children less than 12 years. The majority of 108 (43.2%) cases were in the age group of 30–39 years followed by 70 (28%) in 40–49 years, 48 (19.2%) in 20–29 years, nine (3.6%) in 50–59 years, eight (3.2%) in 0–9 years, four (1.6%) in 10–19 years and three (1.2%) patients were 60 and above years.

There were 170 (68%) males and 80 (32%) females. Patients presented with various clinical symptoms like generalised weakness, fever, cough, loose motion, loss of appetite, skin lesions, oral lesions, breathlessness, herpes zoster, genital lesions and vision problems. None of the patients presented with bleeding. In the present study haemoglobin ranged from 2.3 g/dl to 19.3 g/dl. One hundred and twenty (48%) patients had haemoglobin less than 10 g/dl, 78 (31.2%) had haemoglobin between 10.1-12g/dl and 52 (20.8%) cases had haemoglobin more than 12g/dl. RBC count ranged from 1.02 million/mm³ to 6.78 million/mm³. The majority of cases 207 (82.8%) had RBC count less than 4.5 million/mm³.

Mean corpuscular volume (MCV) ranged from 61.1 to 134.6 fl, mean corpuscular haemoglobin (MCH) from 16.5 to 44.2 picograms and mean corpuscular haemoglobin concentration (MCHC) from 25.9 to 36.2 g/dl. MCV in the range of 80–99 fl was seen in 178 (71.2%) cases and MCH between 27–32 pg in 122 (48.8%) cases indicating normocytic and normochromic nature of RBCs in the majority of patients.

Haematocrit showed wide range of 7% to 57.9%. A maximum of 117 (46.8%) cases had a haematocrit between 31–40%. Red cell distribution width-coefficient of variation (RDW-CV) range was 12% to 27%. 164(65.6%) cases had RDW between 14.1 to 24%.

Total leucocyte count ranged from 1400 to 19100 cells/mm³. One hundred and seventy six (70.4%) patients had normal total leucocyte count, i.e. between 4000 to 10000 cells/mm³. Leucopenia was seen in 52 (20.8%) cases. Leucocytosis (more than 10000 cells/mm³) was seen in 22 (8.8%) cases. Absolute lymphocyte count ranged from zero in one case to 6000 cells/mm³. One hundred and sixty three (65.2%) cases had absolute lymphocyte count less than 1500 cells/mm³ (lymphopenia). Normal absolute



lymphocyte count (1500-4000 cell/mm³) was seen in 81 (32.4%) cases. More than 4000 cells/mm³ was seen in only six (2.4%) cases.

Platelet count ranged from 18,000/mm³ to 6,70,000/mm³. Normal platelet count between 1,50,000–400,000 was seen in 195 (78%) cases. Platelet count less than 1,50,000/mm³ was seen in 45 (18%) cases and more than 400,000/mm³ was seen in 10 (4%) cases.

Anaemia was seen in 210 (84%) cases. The most common pattern of anaemia was normocytic normochromic in 101 (40.4%) cases followed by dimorphic anaemia in 47 (18.8%) cases, normocytic hypochromic anaemia in 29 (11.6%) cases, microcytic hypochromic anaemia in 18 (7.2%) cases and macrocytic anemia in 15 (6%) cases. Pancytopenia was seen in 17 cases. Erythrocyte sedimentation rate in the present study ranged from 5 to 155 mm at the end of first hour. ESR more than 11 mm was seen in 241(96.4%) cases. Mean ESR was 61.2 mm at the end of first hour.

CD4 lymphocyte count ranged from zero to 1274 cells/mm³. CD4 lymphocyte count less than 200 cells/mm³ was seen in 175 (70%) cases, between 200–499 cells/mm³ was seen in 54 (21.6%) cases and more than 500 cells/mm³ was seen in 21 (8.4%) cases. Haematological parameters in HIV patients with different CD4 counts were studied and compared. In patients with CD4 counts less than 200 cells/mm³, 91.4% had anaemia, 26.8% had leucopenia and 21.7% had thrombocytopenia. Observations made in HIV patients with different CD4 counts are shown in Table 1.

Discussion

Haematological abnormalities frequently encountered in HIV-infected individuals are anaemia, granulocyte disorders, thrombocytopenia, lymphomas, coagulopathies and vascular malignancies like Kaposi sarcoma. Although in the majority of cases, haematologic abnormalities are detected in middle or advanced stages of HIV infection, some of these like anaemia and thrombocytopenia have been reported to occur in early stages of HIV infection.⁴

The origin of haematological disorders in HIV infection remain incompletely understood, but has been attributed to dysfunctional haematopoiesis in bone marrow caused by several factors. These include severe nutritional stress in advanced stages of HIV infection, suppression of marrow by invading opportunistic infections or neoplasm, chronic disease associated changes and toxic side effects of antiretroviral compounds (or other medications used to combat the complications of HIV disease). The possibility of HIV directly infecting the haematopoietic precursor cells

and inhibiting their differentiation and development to mature blood cells, has been an attractive hypothesis for the origin of HIV associated dysfunctional haematopoiesis, but to date it remains, to a great extent, an incompletely understood phenomenon.⁴

Table 1: Comparison of haematological parameters in patients with different CD4 counts.

Parameter	CD4->500 cells/mm ³ (n=21)	CD4-200 to 499 cells/mm ³ (n=54)	CD4-<200 cells/mm ³ (n=175)	Statistical test	Remarks (p value)
Anaemia (No of cases)	14 (66.6%)	36 (66.7%)	160 (91.4%)	$\chi^2=23.95$	P <0.0001
Total leucocyte count (mean±SD)	8360 ±3293.9	6773.7 ±3052.2	5246.5 ±2248.1	F=18.80	P <0.0001
Leucopenia (No of cases)	1 (4.8%)	4 (7.4%)	47 (26.8%)	$\chi^2=13.05$	P <0.0001
Abs. lymphocyte count (mean±SD)	2766 ±1260.6	1744 ±687.6	1051 ±554.2	F=74.05	P <0.0001
Lymphopenia (No of cases)	2 (9.5%)	21 (38.9%)	140 (80%)	$\chi^2=62.06$	P <0.0001
Platelet count (mean±SD)	2.8 ±1.04	2.3 ±1.09	2.17 ±1.07	F=3.310	P >0.05
Thrombocytopenia (No of cases)	1 (4.8%)	6 (11.1%)	38 (21.7%)	$\chi^2=5.86$	P >0.05
ESR (mean±SD)	44.2 ±31.03	53.75 ±33.61	65.5 ±32.1	F=5.88	P <0.001

χ^2 =chi square test, F= analysis of variance (ANOVA) test.

The present study aims at recognising the haematological features of HIV infection which is very important with the continuing rise in the prevalence of HIV infection in a developing country like India. In the present study age ranged from 4 years to 65 years and the majority of the patients (156 (62.4%)) were in the age group of 20 to 40 years. There was male predominance, with a male to female ratio of 2.12:1.

In the present study haemoglobin ranged from 2.3g/dl to 19.3g/dl with the mean being 10.2. Kaloutsis et al reported haemoglobin in the range of 3.8 to 17.3g/dl and a mean of



10.8.⁵ However Treacy et al reported a higher mean compared to the present study of 11.34.⁶ The majority (79.2%) of the cases in our study had anaemia with haemoglobin below 12 g/dl.

Table 2: Comparison of number of anaemia cases in present study with others

Authors	No of anaemia cases	Total cases	Percentage
Karcher et al	175	197	89 %
Tripathi et al	61	74	82.4 %
Sitalakshmi et al	27	42	64.2 %
Kaloutsis et al	34	40	85 %
Present study	210	250	84 %

Table 3: Comparison of morphological patterns of blood picture in present study with other studies

Patterns of blood picture	Tripathi et al		Khandekar et al		Present study	
	No.	%	No.	%	No.	%
Normocytic normochromic blood picture	13	17.6 %	-	-	40	16 %
Normocytic normochromic anaemia	54	72.9 %	68	48.57 %	101	40.4 %
Normocytic hypochromic anaemia	-	-	-	-	29	11.6 %
Microcytic hypochromic anaemia	4	5.4 %	15	10.71 %	18	7.2 %
Macrocytic anaemia	3	4.1 %	32	22.86 %	15	6 %
Dimorphic anemia	-	-	25	17.86 %	47	18.8 %
Total	74	100 %	140	100 %	250	100 %

Mean RBC count was 3.66 million/mm³ with a standard deviation of 0.84. Tripathi et al reported a mean RBC count of 3.09 and a standard deviation of 0.36 among 55 AIDS patients. Mean of MCV (mean corpuscular volume) in the present study was 87.3. Tripathi et al reported a mean of 81.81 (N=55 patients).⁷ In the present study the majority of cases 178 (71.2%) had MCV within normal range (80-99 fl) indicating normocytic nature of RBCs.

MCH was 28.4. A similar observation was made by Tripathi et al with a mean of 27.59.⁷ MCHC ranged from 25.9gm/dl

to 36.2gm/dl with the mean being 32.5 and standard deviation of 1.74. One hundred and sixty nine (67.6%) cases had MCHC between 31.5 to 34.5gm/dl indicating normochromasia in the majority of patients.

Mean haematocrit in the present study was 31.33. Tripathi et al reported a mean haematocrit of 27.36.⁷ Mean RDW-CV was 15.7 indicating mild anisocytosis. A similar observation was made by Schneider et al.⁸

In the present study anaemia was seen in 210 (84%) cases. A similar observation was made by Kaloutsis et al in 34/40 (85%) cases.⁵ Karcher et al reported anaemia in 175/197 (89%) patients, and Tripathi et al in 61/74 (82.4%) patients.^{7,9} However Sitalakshmi et al reported anaemia in 27/42 (64.2%) cases which is much lower compared to the present study.¹⁰ Table 2 shows a comparison of number of anaemia cases in the present study with other studies. The most common type of anaemia was normocytic normochromic type in 101 (40.4%) cases. A similar observation was made by Khandekar et al in 68/140(48.57%) cases.¹¹ A comparison of morphological patterns of blood picture in the present study with other studies is given in Table 3.

Mean total leucocyte count was 5827.8 cells/mm³. Kaloutsis et al reported a mean of 5200 cells/mm³.⁵ The majority of 176 (70.4%) cases had a normal total leucocyte count. A similar observation was made by Patwardhan et al in 378/500 (75.6%) cases.¹² Leucopenia was seen in 52 (20.8%) cases. In the present study eosinophilia was seen in 54 (21.6%) cases. Khandekar et al observed eosinophilia in 16/140 (11.43%) cases.¹¹

Lymphopenia (absolute lymphocyte count less than 1500 cells/mm³) was seen in 163 (65.2%) cases. Treacy et al reported lymphopenia in 14/20 (70%) cases.⁶ However Tripathi et al observed a lower number of lymphopenia cases in 19/74 (25.6%) cases.⁷

In the present study thrombocytopenia was seen in 45 (18%) cases. This has been reported by Patwardhan et al in 65/500 (13%) cases and Costello C et al in 121/925 (13%) cases.^{12,13} However Karcher et al reported thrombocytopenia in 88/196 (45%) cases, much higher compared to the present study.⁹ Mean ESR in the present study was 61.2 mm at the end of the first hour indicating high ESR in HIV patients.

CD4 lymphocyte count is essential for assessment of immune status in HIV-infected persons as the pathogenesis of AIDS is largely attributed to a decrease in absolute CD4



cell counts. CD4 cell counts are the criterion for categorising HIV-related clinical conditions by CDC classification system for HIV infection.³ Patients in the present study were divided into three groups based on CD4 lymphocyte count.

Haematological parameters were compared in these three groups (Table 1). The number of cases with anaemia, leucopenia, and lymphopenia increased with reducing CD4 cell counts. Mean total leucocyte count, mean absolute lymphocyte count was lower with reducing CD4 cell counts, and mean ESR increased with reducing CD4 cell counts. These parameters showed significant difference (indicated by p value less than 0.05) between three groups with differing CD4 cell counts. This indicates a higher occurrence of anaemia, lymphopenia and leucopenia with progression of disease. Though there was a difference in mean platelet count between these three groups, it was not statistically significant, indicating occurrence of thrombocytopenia independent of disease progression.

Anaemia in HIV-infected patients is likely to be multifactorial. Inflammatory cytokines play a central role in the pathogenesis of anemia. TNF, IL-1 and interferon gamma have all been shown to inhibit erythropoiesis in vitro.¹⁴ TNF levels have been shown to be consistently elevated in HIV infection and correlate with viral load.¹⁵ Dyserythropoiesis and opportunistic infections also result in certain haematologic abnormalities.¹⁶ Severe anaemia has been reported to be present in 76% of patients with disseminated mycobacterium avium complex (MAC) disease.¹⁵ Chronic pure red cell aplasia has been reported to occur in HIV-infected patients with parvovirus B19 infection.¹⁷ Anaemia in HIV-infected patients is known to occur as an adverse effect of drug therapy for HIV infection or its complications. Myelosuppression mainly macrocytic anaemia is the dose limiting toxicity of zidovudine. Other drugs that are associated with anaemia in AIDS patients include primaquine, dapsone and ganciclovir.¹⁵

Leucopenia generally correlates with the severity of a clinical syndrome like anaemia.¹⁸ Reduction in absolute number of CD4 T cells occurs as one of the earliest immunologic abnormalities of HIV infection and is the most important prognostic indicator for risk of developing opportunistic infections.¹⁴

The mechanism of thrombocytopenia in HIV infection appears to involve increased platelet destruction and ineffective platelet production. Most reports indicate that there is significant platelet sequestration and destruction in the spleen in HIV-associated thrombocytopenia. Platelet destruction is predominant early in the course of disease,

whereas decreased platelet production is the predominant factor later in the course of the disease. Antibodies directed against platelet glycoprotein IIIa, similar to those seen in classic ITP are seen.¹⁴ Megakaryocytes express CD4 and CXCR4 and are susceptible to infection by HIV. Studies of megakaryocytes from HIV-infected patients have shown viral RNA and proteins suggesting that these cells are infected in vivo.¹⁹ Other causes include marrow infiltration by opportunistic infection or lymphoma, TTP, and myelosuppressive effects of drug therapy.¹⁵

Drugs used to treat HIV infection and other infections associated with HIV frequently cause haematologic toxicity. Several in vitro studies have shown that zidovudine and dideoxycytidine inhibit erythroid colony forming units (CFU-E) and granulocyte macrophage colony forming units. Zidovudine is phosphorylated to an active triphosphate moiety by mammalian enzymes and the resulting metabolite may be responsible for inducing toxicity. Ganciclovir causes leucopenia. Pyrimethamine and sulfadiazine used in the treatment of toxoplasmosis causes leucopenia and thrombocytopenia. Chemotherapeutic agents used in the treatment of malignancies result in myelosuppression which is often dose limiting. Alpha interferon used in the treatment of Kaposi sarcoma is frequently associated with haematologic toxicity.²⁰

Conclusion

Haematologic manifestations are common in HIV-infected patients. Anaemia is the most common manifestation and the most frequent form is normocytic and normochromic type. Significant numbers of patients also show lymphopenia and thrombocytopenia. Incidence of anaemia and leucopenia correlates with disease progression. Thrombocytopenia occurs independent of disease progression. The present study also showed significant correlation of absolute lymphocyte count with CD4 cell counts. Thus absolute lymphocyte count can be used as a predictor of CD4 counts and can be used to assess the stage of the disease in centres where CD4 count evaluation is not available. At the same time patients with HIV infection should be investigated and treated for haematological abnormalities to reduce the morbidity of the patient.

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