



Original Research Article

Hematological Abnormalities in Febrile HIV-Infected Patients and Factors Related to Them

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ABSTRACT

Hematological abnormalities, such as anemia, neutropenia, and thrombocytopenia, are commonly observed in patients infected with HIV. The aim of the study was to evaluate the frequency of hematological abnormalities in HIV patients, and to evaluate the correlation of them with CD4 cell number.

Methods: Cross-sectional retrospective study. Multiple logistic regression methods were used to identify risk factors for hematological abnormalities.

Results: A total of 82.4% of patients (108/131) had anemia at the moment of evaluation. The prevalence of anemia was 83.3% in female patients and 82.1% in male persons. 89% of patients had anemia in the low CD4 group and 52.9% in the high CD4 group ($p = 0.001$). In multivariate logistic regression analysis CD4 < 200 cells/mm³ had large independent associations with anemia, and HAART use decreases the risk of anemia. Lymphopenia was noted in 63.4%, neutropenia in 2.29%, and thrombocytopenia in 6.1% of the patients.

Conclusions: Anemia was more common than neutropenia or thrombocytopenia in the HIV-infected patients. In view of the high prevalence of haematological disorders among HIV patients, it is strongly recommended that all HIV patients be investigated and treated for these disorders.

Key words: hematological abnormalities, anemia, febrile, HIV-infected, HAART, risk factor

INTRODUCTION

Acquired Immune Deficiency Syndrome (AIDS) is caused by the Human Immunodeficiency Virus (HIV) and is characterized by progressive damage to the body's immune system which results in a number of opportunistic infections, immunological and hematological complications. ^[1] Hematological abnormalities, such as anemia, neutropenia,

and thrombocytopenia, are commonly observed in patients infected with HIV. ^[2,3]

The prevalence of anemia in patients with HIV infection varies widely by sex and race/ethnicity, with rates ranging from 30% in asymptomatic HIV to as high as 63-95% in persons with AIDS. ^[4-8] The causes of HIV-related anemia are multifactorial. ^[9, 10-13] HIV may directly affect bone marrow stromal cell or cause cytokine secretion,

leading to decreased production of red blood cells (RBCs) and other bone marrow elements. The important causes of anemia in HIV infection are defective iron metabolism and reutilization, nutritional deficiencies, opportunistic infections, ART (antiretroviral therapy), administration of chemotherapeutic agents and advanced stage of disease with its complications. [14]

Anemia as the most frequent hematological abnormality in patients infected with HIV has been associated with impaired quality of life, [15-17] accelerated progression of the disease, and a higher mortality rate. [18-22] Previous studies have demonstrated that patients with HIV infection and low hemoglobin levels have a higher mortality risk than less anemic comparison groups, even after controlling for CD4 cell count and viral load. [18,19,23,24]

Anemia is associated with thrombocytopenia and neutropenia, perhaps because myelosuppression may affect production of all the cell lineages. In one early series of patients with AIDS, lymphopenia was noted in 70%, neutropenia in 50%, and thrombocytopenia in 40% of the patients. [25]

There is paucity of data from Albania on the hematological manifestations of HIV, which prompted us to conduct this study. We assessed 131 febrile HIV-infected individuals to look for various hematological manifestations.

The objective of this cross-sectional retrospective study was to evaluate the frequency of hematological abnormalities in febrile HIV patients, and to evaluate the correlation of these hematological abnormalities with CD4 cell number. We also aimed to evaluate the impact of HAART treatment on hemoglobin concentration levels and on anemia.

MATERIALS AND METHODS

Among 242 HIV-infected patients admitted to the University Hospital Centre

of Tirana “Mother Theresa “ during December 2009 - January 2011 were selected 131 cases that fulfilled our study inclusion criteria: ≥ 15 years old, febrile, HIV-infected. The analyses recorded were RBC count, hemoglobin level, white blood cell (WBC), lymphocyte, neutrophil, and platelet counts.

Anemia was defined as hemoglobin < 13 g/dl for men and < 12 g/dl for women. [26] The various degrees of anemia were classified using hemoglobin values of 11.0 – 12.0/13.0 g/dl (female/male): Mild anemia; 8.0 – 10.9 g/dl: Moderate anemia and below 8.0 g/dl: Severe anemia respectively. [26] Leucopenia was defined as total WBC count less than 2000 cells/ μ l; neutropenia was defined as neutrophil count $< 40\%$; lymphopenia was considered when lymphocyte count was $< 30\%$ and thrombocytopenia was defined as total platelet count of $< 100 \times 10^3$ / μ l. [27,28]

Absolute CD4 cell count analysis was carried out by flowcytometry. The patients were divided into two groups according to their CD4 count: low CD4 (< 200 cells/ μ l) and high CD4 (≥ 200 cells/ μ l). Also was recorded if the patients were in highly active antiretroviral therapy (HAART) or not. [29]

This study was carried out in accordance with the Helsinki Declaration of 1975, as revised in 2000, and was approved by the ethics committee of our institution. As this was a retrospective and cross-sectional analysis, the local committee exempted the authors from the need to apply for informed consent.

Statistical analysis

SPSS, version 15 statistical software was used for analysis. The results are presented as mean and standard deviation (SD). Unpaired t-test was used to compare the means of all continuous variables. Multiple logistic regression methods were used to identify risk factors for hematological

abnormalities. The results were reported as odds ratio (OR) and 95% CI (confidence interval). A p-value of < 0.05 was considered to be statistically significant.

RESULTS

The mean age of 131 HIV-infected patients was 42.13 ± 11.25 yrs (figure 1). 77.1% of the patients were males and 22.9% were females.

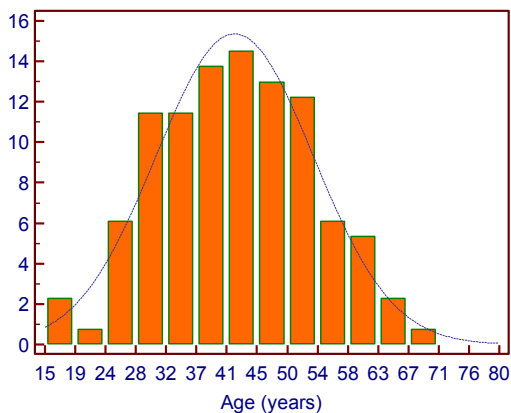


FIGURE 1. Histogram of distribution of patients according to the age (years).

TABLE 1. Description of the patient population.

Variables	Value
Gender (M/F; n/%)	101/30; 77.1%/22.9%
Age (years)*	42.13 ± 11.25 (15-71)
CD4 < 200/CD4 ≥ 200 (%)	81.1%/18.9%
Hemoglobin (d/dl)*	
Male	10.76 ± 2.55 (3.2 - 26.6)
Female	10.06 ± 2.05 (6.9 - 14.5)
Platelet count (x 10 ⁹ /l)*	242.373 ± 116.632 (23.000 - 768.000)

*Values are mean ± standard deviation, (range)

CD4 values were recorded only in 90 cases, the low CD4 group comprised 73 patients (81.1%) and the high CD4 group 17 patients (18.9%) (p < 0.0001). Mean CD4 cell count was 128.44 ± 132.95 (range 0-576) (table 1). 63 patients (48%) were receiving HAART while 69 patients (52%) were not receiving HAART. 25 patients (32.7%) were diagnosed for the first time as HIV-infected patients, from them 22 patients (88%) had CD4 < 200 cells/μl.

A total of 82.4% of patients (108/131) had anemia at the moment of evaluation. The prevalence of anemia was 83.3% in female patients and 82.1% in male persons (figure 2, figure 3), 89% of patients had anemia in the low CD4 group and 52.9% in the high CD4 group (p = 0.001), (figure 4). The mean ± standard deviation hemoglobin concentrations were 10.07 ± 2.38 g/dl (3.2-15.5) and 12.18 ± 2.02 g/dl (8.8-15) for patients in the low and high CD4 cell count groups, respectively (p = 0.001). Hemoglobin levels showed statistically significant correlation with CD4 counts. In multivariate logistic regression analysis CD4 < 200 cells/mm³ had large independent associations with anemia (OR = 7.22, 95% CI: 2.16-24.04, P = 0.001). Also in multivariate logistic regression analysis, HAART use decreases the risk of anemia (OR = 0.24, 95% CI: 0.07-0.77, P = 0.009). Anemia was an independent risk factor for mortality: OR = 4.10, 95% CI: 0.51-32.56, P = 0.10. Prevalence of anemia among survivors was 80.5% and among non-survivors 94.4%, P = 0.26.

The mean ± SD neutrophil counts were 66.12% ± 16.32% (22.2-87.9) and 67.5% ± 13.16% (39.3-86.5) for the low CD4 and high CD4 groups, respectively (p = 0.74). Only 3 patients (2.29%) were presented with neutropenia.

The mean ± SD platelet counts were [246.435 ± 122.455 (23.000-606.000)] x 10⁹/l and [258.875 ± 81.665 (134.000-479.000)] x 10⁹/l for the low CD4 and the high CD4 groups, respectively (p = 0.69). only 8 patients (6.1%) were presented with thrombocytopenia and 83 patients (63.4%) were presented with lymphopenia, 9.2% of the patients (12/131) were with leucopenia (Table 2).

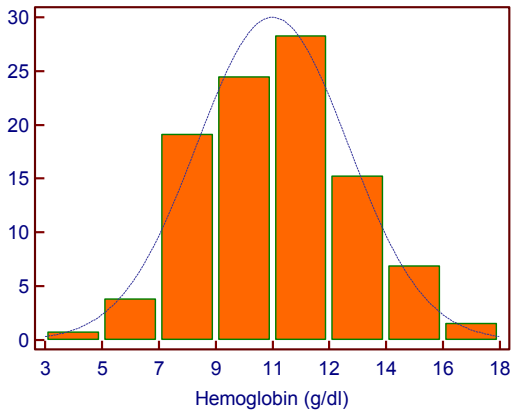


FIGURE 2. Histogram of distribution of patients according to the hemoglobin levels.

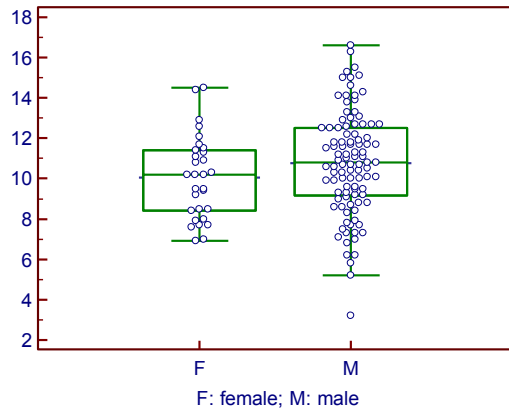


FIGURE 3. Hemoglobin levels according to the sex.

TABLE 2. Haemogram and hematological abnormalities according to the CD4 count group

	CD4 < 200	CD4 ≥ 200
Number of the patients	73	17
Hb value (g/dl)*	10.07 ± 2.38 (3.2-15.5)	12.18 ± 2.02 (8.8-15)
Anemia n (%)*	65/73 (89%)	9/17 (52.9%)
Platelet (x 10 ⁹ /l)**	246.4 ± 122.4 (23.0-606.0)	258.8 ± 81.6 (134.0-479.0)
Neutrophil (%)**	66.12 ± 16.32 (22.2-87.9)	67.5 ± 13.1 (39.3-86.5)
Lymphocyte (%)**	27.24 ± 14.96 (2.7-71.7)	27.26 ± 12.03 (10.5-53.7)
Lymphopeni n (%)**	7/36 (19.4%)	10/54 (18.5%)

*P < 0.05

**P > 0.05

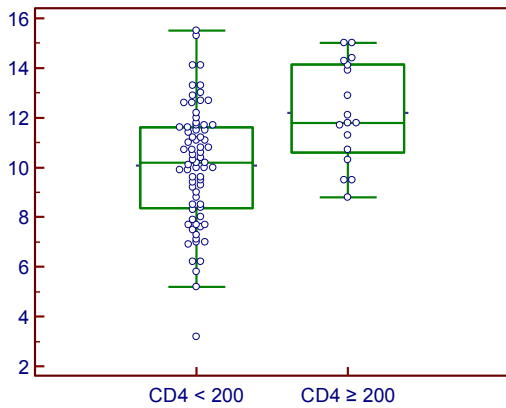


FIGURE 4. Hemoglobin levels according to the CD4 count group.

TABLE 3. Patients' distribution according to the degrees of anemia.

	Hemoglobin levels	Number (%)
No anemia	Hb > 13 g/dl	23 (17.6%)
Mild anemia	Hb: 11.0 -12.0/13.0 g/dl	35 (26.7%)
Moderate anemia	Hb: 8 - 10.9 g/dl	51 (38.9%)
Severe anemia	Hb < 8 g/dl	22 (16.8%)

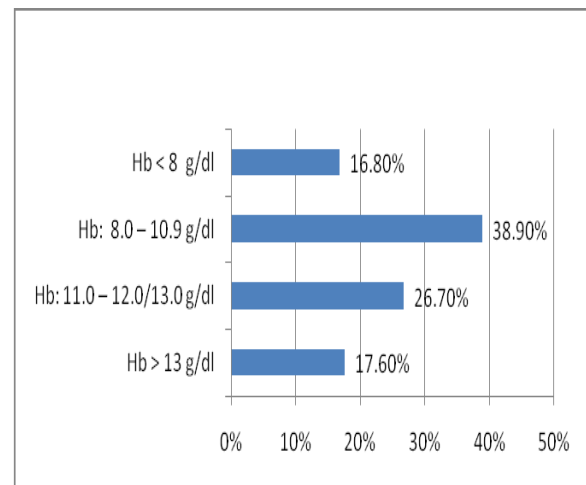


FIGURE 5. Distribution of the patients according to the degrees of anemia.

DISCUSSION

Hematological abnormalities are among the most common complications of HIV. These involve all lineages of blood

cells and cytopenias are most frequent during the advanced stage of disease. ^[30]

In different study settings, the prevalence of anemia in persons with acquired immunodeficiency syndrome has been estimated at 63% to 95%, ^[5-8] making it more common than thrombocytopenia or leucopenia in patients with AIDS. ^[6,31] In the present study anemia was the most common presentation. Among 131 HIV-infected individuals 108 (84.2%) were found to be anemic. In a study by Mir et al on a cohort of 60 HIV infected individuals reported anemia, thrombocytopenia, leucopenia and various permutations of these in majority of individuals. ^[6] The highest rate of anemia occurs in patients with advanced HIV disease. The prevalence of anemia was strongly and consistently associated with the progression of HIV disease measured by CD4 count of < 200 cells/ μ l. This association is most likely explained by the increasing viral burden as HIV disease progresses, which could cause anemia by increased cytokine-mediated myelosuppression. In our study 81.1% of cases were with CD4 counts < 200 cells/ μ l, while 18.9% of the patients were with CD4 \geq 200 cells/ μ l and there was statistically significant difference ($p < 0.0001$) between both groups. As expected, patients from the group with low CD4 count presented a significantly increased rate of anemia compared to patients from the group with high CD4 counts (89% vs. 52.9%, $p = 0.001$). Our multivariate models showed CD4 count to be significant independent risk factor for anemia. CD4 cell count and/or AIDS have been found to be significant variables that contributed to the incidence of anemia in other recent studies. ^[16,17,32,33]

As Belperio and Rhew ^[23] reported in their systematic review of 31 articles, anemia rates in studies of patients with HIV infection varied widely and increased with the severity of illness of the HIV-infected

population studied and the Hb level used to define anemia. In the present study severe anemia was observed in 16.8% of the patients.

The administration of ZDV is recognized to cause anemia because of myelosuppression. ^[34] In our analysis, the prescription of ZDV was not associated with anemia.

Highly active antiretroviral therapy (HAART) has been shown to reduce anemia by inhibiting the progress of the disease. ^[35] HAART decreases viral load, which may result in decreased activity of immune effectors, thus ameliorating anemia by reversing the anti-proliferative effects of cytokines. In the present study HAART decreased the risk for anemia, prevalence of anemia was lower in HAART treated patients compared to other patients (76.1% vs. 92.9%, $p = 0.02$, respectively).

The rate of anemia wasn't higher among women than among men, in contrary with some studies in the USA that have shown that female gender is risk factor for anemia. ^[33,36]

Our study showed that anemia wasn't associated with thrombocytopenia, leucopenia, lymphopenia and neutropenia.

Thrombocytopenia is known to be frequent complication of HIV infection. ^[30] In our study only 6.1% of the patients have thrombocytopenia. Patients with a more severe disease (CD4 < 200 cells/ μ l) presented a slightly lower platelet count (p non-significant). The mean neutrophil count wasn't lower in the group of patients with low CD4 cell counts, a finding that is in contrary with the literature. ^[37,38]

CONCLUSION

Anemia was more common than neutropenia, leucopenia or thrombocytopenia in the HIV-infected patients. In view of the progressive increases of HIV in our population and the high prevalence of

hematological disorders among HIV patients, it is strongly recommended that all HIV patients be investigated and treated for these disorders. Proper treatment of HIV-related anemia is a critical component of healthcare management for HIV-infected patients.

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wrote the paper; AH: collected data, wrote the paper, NÇ: collected data, wrote the paper, AP collected data, wrote the paper, DHK participated in the study design and revised the paper critically for important intellectual content. Each author approved the final version for publication.

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