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A Study Of Factors Associated With Anemia In HIV Infected Individuals In A Tertiary Care Hospital.

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ABSTRACT

Anemia is the most common hematologic manifestation seen in HIV infection. The etiologies of anemia may be different from the general population. The objectives of the study were to study the etiology of anemia in HIV positive individuals and to study the relationship between anemia and immunological status as indicated by the CD4 count. This was a cross sectional study done among sixty HIV positive patients with anemia admitted in medical wards of Department Of General Medicine, Government Medical College& Hospital, Krishnagiri, Tamil Nadu India In the year 2021-2022. CD4 count was lesser than 200/µl in 58.3% of patients. Fifty one percent of the patients were on HAART. Among the patients on HAART 67% were on zidovudine .16.7% of patients had grade one anemia,31.7% of percent had grade two anemia, 18.3% of percent had grade three and 33.3% of percentage had grade four anemia. Seventy percent had their MCV in normal range, 16.7% percent had MCV less than 76 fl and 13.3% had MCV greater than 96 fl. Most patients had anemia of chronic disease in comparison to other etiologies. 51.7% percent had anemia of chronic disease, 15% had B12/folate deficiency, 10% had bone marrow infiltration, 10% had iron deficiency anemia, 10% had zidovudine induced anemia and 3.3% had anemia due to hemolysis.

Keywords: AIDS, Anemia, HIV, HAART, Hemoglobin, Lymphoma, MCV, CD4 count, B12 deficiency.

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INTRODUCTION

AIDS was first identified in the United States way back in 1981predominantly in people having monogamous relationship, and Human Immunodeficiency Virus was later detected as the causative organism. While starting it is limited, infection with the human immunodeficiency virus increased rapidly over the last half a century to become the most deadliest epidemic in the whole world. According to December 2009, 33.1 million people were approximated to be infected and living with HIV/AIDS, and more than 35.1 million had died from the beginning in the epidemic [1].

Asia is the rapidly increasing in the HIV infected people and majority found in the sub- Saharan Africa. Profound immunodeficiency is found in HIV infected individual is hallmark of HIV due to progressive decline in helper T cells.CD4 cells decline in number below a certain level is high risk for various opportunistic diseases to develop in particularly neoplasia and infection that in AIDS defining illnesses [2]. Detection of Human Immunodeficiency Virus by tracing its antibodies and also direct detection of Human Immunodeficiency Virus or its components helps for the diagnosis of HIV infection. ELISA is used for screening testfor HIV infection and confirmatory by WESTERN BLOT. The best indicator for patients with HIV infected is identified as CD4 + T cells level in laboratory test and to know immunologic competence in same patient. Human immunodeficiency virusfound to be etiology for broad spectrum of infectious, neoplastic and immunologic complications. Followed diseases are major concern in HIV course and anemic are also observed may complicate the all condition in HIV patients [3,4]. Anemia is rarely a fatal complication; however it does significantly increase the morbidity as well as precipitates preexisting illnesses. Hence these patients found to be reduced survival in high-risk Human Immunodeficiency Virus patients [5]. The prevalence of anemia in patients with Human Immunodeficiency Virus varies between 10% in asymptomatic patients to 92% in persons with full blown AIDS In Human Immunodeficiency Virus patients, anemia is a predictive feature of disease progression or death, independent of CD4 and viral load. Anemia impacts a range of dimensions of quality of life [6]. The common causes of anemia in HIV and non-HIV patients are varied so treatment will differ. By knowing knowledge of the association of anemia and HIV infection is important it helps in treatments for anemia are available including r-human erythropoietin, blood transfusion, and in drug causing anemia, terminating of myelosuppressive therapies. Hence knowledge of the pathophysiological mechanisms and the prevalence of various causes of anemia will help us in treatment of anemia in HIV positive patients. Very few studies have examined factors associated with anemia in the setting of a developing country [7].

METHODS

This was a descriptive cross-sectional study done during the period of April 2021to September 2022 on 60 consecutive HIV patients in different stages of disease seen as inpatients in medical ward Department Of General Medicine, Government Medical College& Hospital, Krishnagiri, Tamil Nadu India All respondents were adults, aged more than 18 yrs. Informed consent was taken prior to inclusion in the study.

Inclusion Criteria

- HIV positive patients
- Anemia with hemoglobin less than 10.9gm/dl

Method Of Collection Of Data

All patients were interviewed and examined by the investigator. A Proforma, which is appended in the annexure, was used for the above purpose.

Tests

HIV was confirmed by the ELISA test. CD4 counts were analyzed using the Flowcytometry method. Hemoglobin, total count and differential count were performed in the laboratory using automated counting chambers and confirmed manually. Further work up for anemia including reticulocyte count, peripheral smear examination, mean corpuscular volume estimation, direct coombs test, serum ferritin and B12 levels were done. Bone marrow aspiration was done for most of the patients

as part of anemia evaluation. Other tests were done as per the needs of the patient.

Statistical Methods

Statistical analyses was performed with SPSS. Normal data were summarized using mean and standard deviation (SD) and non-normal data using median and interquartile range. Correlation coefficient was be used to compare hemoglobinvalues and CD4 counts.

RESULTS

Demography

Table 1: Age Distribution

AGE_GROUP	FREQUENCY	PERCENT
20 - 30 YEARS	9	15.0
31-40 YEARS	17	28.3
41 - 50 YEARS	27	45.0
51-60 YEARS	7	11.7
Total	60	100.0

Sixty Patients With HIV Infection And Anemia Were IncludedIn The Study. Minimum Age Was 22 Years And Maximum Age Was 60 Years (Mean ± Sd: 41.23±8.52) 70% (42) of the subjects were male and 30% (18) were female.

Table 2: Duration Since Diagnosis

DURATION	FREQUENCY	PERCENT
< ONE MONTH	20	33.3
ONE - 12 MONTHS	29	48
> TWELVE MONTHS	11	18.7
Total	60	100.

Table 3: Distribution Of CD4 Counts

CD4 COUNTS	FREQUENCY	PERCENT
< 200	35	58.3
> 200	25	41.7
Total	60	100.0

58.3% Patients Have <200 And 41.7% Patients >200, Mean Cd4 CountValue Around 194

Table 4: Frequency Of Patients On ART

ART	FREQUENCY	PERCEN
N	24	40.0
Y	36	60.0
Total	60	100.0

Table 5: Frequency Of Patients On ZDV

ZDV	FREQUENCY	PERCENT
N	12	33%
Y	24	67%
Total	36	10 .0

Among the patients on ART 67% was on zidovudine and the remaining 33% other NRTI on stavudine. there were no patient on any.

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Table 6: MCV Levels

MCV	FREQUENCY	PERCENT
< 76	10	16.7
76-95	42	70
> 96	8	13.3
Total	60	10 .00

The mean corpuscular volume was 89.2fl (range59-125fl) 70% had their mcv in normal range, 16.7 less than normal,13.3 had more than normal. Only 50% patients with vitamin b12 deficiency had macrocytes. In peripheral smear 70% patients had normocytic normochromic anemia, 22%had microcyticanemia, anisopoikilocytes was noted in 60% and tear drop in40% of patients.

Table 7: Leukopenia In HIV Patients

TC	FREQUENCY	PERCENT
< 4000	32	53.3
> 4000	28	46.7
Total	60	10 .00

53.3% Had leukopenia and 46.7% had normal leukocytes

Table 8: Direct Coombs Test

DCT	FREQUENCY	PERCENT
N	51	85.0
P	9	15.0
Total	60	100.0

15% of the patient had positive direct Coombs test. Only 3% had evidenced of hemolysis (high LDH levels, unconjugated hyper bilirubinemia)

Table 9: Peripheral Smear Evaluation

PS	FREQUENCY	PERCENT
Mg A	8	13.3
MNA	11	18.3
NNA	41	68.3
Total	60	100.0

MgA-megaloblastic, MNA-microcytic, NNA-normocytic anemia 13.3% Had megaloblastic picture, 18.3 % 68.3% HAD normocytic picture HAD microcytic.

Table 10: Grades Of Anemia

GRADE OF ANEMIA	FREQUENCY	PERCENT
GRADE I 9.5-10.9	10	16.7
GRADE II 8-9.4	19	31.7
GRADE III 6.5- 7.9	11	18.3
GRADE IV <6.5	20	33.3
Total	60	100.0

16.7% HAD grade one, 31.7% hadthree, 33.3% HAD grade four grade two, 18.3% HAD grade

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Table 11: Thrombocytopenia In HIV Patients

PLATELETS COUNT	FREQUENCY	PERCENT
< ONE L KHS	7	11.7
> ONE L KHS	53	88.3
Total	60	100.0

11.7% HAD < one lakh and 88.3% HAD > one lakhs

Table 12: Reticulocyte Proliferation Index

RPI	FREQUENCY	PERCENT
< 2.5	58	96.7
> 2.5	2	3.3
Total	60	100.0

96.7% associated with < 2.5 and 3.3% associated with > 2.5

Table 13: Vitamin B12 Level

Se. B12	FREQUENCY	PERCENT
L	9	15.0
N	51	85.0
Total	60	100.0

85% have normal level and 15% HAD low level, there is no correlation between B12 and CD4 count and hemoglobin

Table 14: Serum Ferritin Level

Se. FERRITIN	FREQUENCY	PERCENT
< 24	2	3.3
> 24	58	96.7
Total	60	100.0

% HAD low serum ferritin levels in our study no correlation between S. ferritin and CD4 count and haemoglobin. Though10% of patients our study had iron deficiency anemia, only 3.3% had low ferritin levels

Table 14: Correlation Between Hb and ZDV

ZDV	FREQUENCY	PERCENT
N	16	45%
Y	20	55%
Total	36	100.0

Table 15: Etiology Of Anemia

ETIOLOGY	FREQUENCY	PERCENT
Anemia chronic disease (inflammation)	31	51.7
Anemia secondary to bone marrow infiltration	6	10.0
Iron deficiency anemia	6	10.0
B12/Folate deficiency anemia	9	15.0
Zidovudine Induced anemia	6	10.0
Anemia secondary to hemolysis	2	3.3
Total	60	100.0

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Hypoproliferative anemia's is characterized by low reticulocyte production index normocytic, normochromic red cells, although microcytic, hypochromic cells may be observed. Causes are (1) marrow damage, (2) iron deficiency, (3) inadequate EPO stimulation- impaired renal function, suppression of EPO production by inflammatory cytokines such as interleukin 1, or reduced tissue needs for O2 from metabolic disease such as hypothyroidism. Maturation defect is characterized by low reticulocyte production index, macro- or microcytosis on peripheral blood smear. Bone marrow examination shows erythroid hyperplasia. Causes are nuclear maturation defects, associated with macrocytosis and abnormal marrow development or cytoplasmic maturation defects, associated with microcytosis and hypochromia usually from defects in hemoglobin synthesis. Hemolytic anemia is characterized by increased reticulocyte proliferation index.

Table 16: CD4 Count And Etiology Of Anemia

CD4 COUNT	N	Mean	Std. Deviation	Std. Error	Minimum	Maximum
Hypo proliferative Anemia	45	158.0667	102.63293	15.29961	50.00	608.00
Maturation defect	13	281.7692	202.17078	56.07209	18.00	658.00
Hemolysis	2	270.0000	212.13203	150.00000	120.00	420.00
Total	60	188.6000	140.64033	18.15659	18.00	658.00

t= 4.794*p=0.012

DISCUSSION

In this study 60 consecutive patients infected with HIV (42 males and 18 females) and anemia who were admitted to the medical wards were included. Patients with mild anemia (>10.9g/dl) were excluded from the study. Only patients with hemoglobin less than 10.9 gm/dl (more than grade one of WHO/ACTG criteria) were included in the study. Minimum age of the subjects was 22 years and the maximum age was 60 years (Mean ± SD: 41.23±8.52). 70% of the subjects were male and 30% were female. Mean age in males was 42.5(SD 8.8) years and in females was 39 (SD 8.0) years. The disease was seen affecting people in the most productive years of their live [8]. These demographic data are similar to those documented in other studies done in India88. 88.3% percent of patients were married. The unmarried patients (11.7% of the total) were all males. Males have commonly acquired the disease through premarital and extramarital sexual contact, whereas females have mostly acquired the disease from their spouses [9]. Females have generally been diagnosed as HIV positive during either routine or ante natal checkups or when their husbands came with opportunistic infections. Majority of our study population were from Tamil Nadu and adjoining part of Andhra Pradesh. Madras medical college is a major referral center for patients from these areas. Patients from Tamil Nadu and part of Andhra utilize the services of this hospital and the study can be considered as done in a South Indian population. Among the patients in the study 81.3%had their diagnosis established within 1 year of this study and 18.7% had their diagnosis established greater than one year ago. This was much lesser compared to other standard studies. The mean CD4 count was 193/µl. Mean CD4 count in males was 199/µl and in females was 200/µl [10]. CD4 count was lesser than 200/µl in 58.3% of patients and was greater than 200/µl in 41.7% of the patients. These features were similar to the other studies done in South India. [99] Thus the patients included in this study had advanced disease. 60% percentage of the patients were on HAART. Among the patients on HAART 67% were on zidovudine and the remaining 33% were on stavudine along with lamivudine and an NNRTI [11]. There were no patients on any other NRTI. 75% of the total patients were on co-trimoxazole therapy. Severity of anemia was classified according to ACTG/WHO grading. 16.7% had grade one, anemia, 31.7% had grade two,18.3% had grade three and 33.3% had grade four anemia [12]. Among our patients 53.3% had associated leucopenia and 11.7 % had associated thrombocytopenia. The prevalence of neutropenia ranges from 0.8% to44% and thrombocytopenia ranges from 8% to 30% in patients with HIV according toother studies done by Zon et al and Murphy [77] et al. The mean of mean corpuscular volume (MCV) was 89.2fl (Range 59-125fl). Seventy percent had their MCV in normal range. Seventeen percent had MCV less than 76 fl and 13% had MCV greater than 96 fl [13]. Sixty percent of patients with MCV less than 76 fl had iron deficiency anemia. Thus 40% of patients with low MCV had etiology of anemia other than iron deficiency & microcytosis cannot be taken as indicative of iron deficiency. Among the patients with macrocytosis 87.5% had B12/folate deficiency and 12.5% had zidovudine induced anemia [14]. Macrocytosis is commonly attributed to NRTI therapy but in our study majority of these patients had a low levels of vitamin B12 or folic acid.96.7%of patients

had reticulocyte proliferation index (RPI) less than 2.5. The mean RPI was 0.71(Range 0.03- 4.40) [15]. This indicates that majority of these patients have hypoproliferative marrow due to various causes.15 %of the patients had positive direct antiglobulin (Coomb's) test (DCT). However, only 3% had evidence of hemolysis (high lactate dehydrogenase levels; unconjugated hyperbilirubinemia). This finding is similar to the results of another study by Ellaurie et al which showed DCT positivity in 37% of HIV- persons but clinically not significant hemolysis [16]. This indicates that positive DCT in HIV infection may simply be a results of polyclonal hypergammaglobulinemia which is common in HIV infection & may not necessarily mean hemolysis. In our study 15% had low vitamin B12 levels. According to Paltiel et al laboratory findings in HIV sero positive individuals shows vitamin B12 decreased in up to 30% [17]. Falling CD4 counts were correlating with low vitamin B12 levels in this study. However, in our study there was not significant relation betweenvitamin B12 levels and CD4 count or Hb. In our study there was no related correlation between serum ferritin levels and CD4 count or hemoglobin. Even in the presence of absolute iron deficiency serum ferritin levels may be elevated in HIV infection because of chronic inflammation [18]. Though 10% of patients in our study had absolute iron deficiency manifested by grade zero iron stores in the bone marrow only. 3.3%of patients had low serum ferritin levels. All patients with low ferritin levels had iron deficiency. Thus normal ferritin level does not rule out iron deficiency in HIV positive patients as ferritin is known as acute phase reactant & gets increased in inflammatory states [19]. Most patients in our study had high serum ferritin levels. Riera et al reported a high prevalence of elevated serum and red cell ferritin levels in 168 patients with HIV infection. High serum ferritin levels were found to correlate with clinical worsening of infection and with decreasing CD4+ lymphocyte counts ($p < 0.001$) in this study [20]. Bone marrow was particularly examined for cellularity, dysplasia, and fibrosis, infiltration by infectious agents or malignant cells and iron staining [21]. Common histopathological features, suggestive of HIV infection but non- pathognomonic as reported in other studies were hypocellularity, dysplasia, and lymphocytic and histiocytic infiltrates with or without granulomas, reticular fibrosis and increased iron deposits. An attempt was made to look for any relationship between immunological status as indicated by CD4 count and anemia as indicated by hemoglobin levels [22]. Many prospective and cross-sectional studies have shown a good correlation between Hb and CD4 counts [23]. This association is most likely explained by fact that disease progression could be associated with cytokine mediated myelosuppression. However various factors not related to disease progression may interfere in the direct relationship between CD4 count and hemoglobin including antiretroviral therapy, blood loss etc. and need to be excluded as in the above study. There may be no correlation between hemoglobin and anemia if all the etiologies of anemia are included as in our study [24]. Mean CD4 (119/µl) in patients who had anemia of chronic disease is significantly lesser than mean CD4 (270/µl) in patients who had anemia due to other etiologies ($p<0.001$). Among patients with low immunological status as expressed by CD4 count less than 200/µl, the etiologies of anemia were anemia of chronic disease (51.7%), anemia secondary to bone marrow infiltration (10.0%), B12/folate deficiency and zidovudine induced anemia (25%) [25]. In patients with CD4 count greater than 200/µl, the most common etiologies of anemia were iron deficiency (26.1%), Vitamin B12/folate deficiency and zidovudine induced anemia (39.1%), anemia of chronic disease (26.1%) & anemia secondary to hemolysis (8.7%) [26]. There were no cases of anemia secondary to bone marrow infiltration. All patients with bone marrow infiltration had CD4 count < 200/µl, and thus bone marrow examination was very important in patients with low CD4 count. In patients with CD4 count > 200/µl, anemia in chronic disease was less common and other etiologies were comparable to HIV negative patients [27-30].

CONCULSION

In this study, sixty patients with HIV infection and anemia were studied to find the etiology of anemia in HIV infected patients and find the relationship between anemia and immunological status as mention by the CD4 count. Only patients with Hb less than 10.9 g/dl (more than grade I of WHO/ACTG criteria) were included in this study.CD4 count was lesser than 200/µl in 58% of patients and was greater than 200/µl in 42% of the patients. Thus the patients included in this study had advanced disease. Mean CD4 count in males was 199/µl and in females were 200/µl. Sixty percent of the patients were on HAART. Among the patients on HAART 67% were on zidovudine and the remaining 33%were on stavudine along with lamivudine and an NNRTI.16.7% had grade oneanemia,31.7% had grade two anemia, 18.3% had grade three and 33.3% had grade four anemia. This is probably because our study was done in a tertiary care hospital and majority of the patients had advanced disease. Fifty three percent had associated leucopenia and 11.7% had associated thrombocytopenia. Seventy percent had their MCV in normal range. Seventeen percent had MCV less than 76 fl and 13% had MCV greater than

96 fl. On peripheral smear, 68.3% of the patients had normocytic normochromic anemia. Microcytes were present in 13.3% and 13.4% had macrocytes. Peripheral smear is more sensitive than MCV in the evaluation of anaemia. Sixty percent of patients with MCV less than 76 fl had iron deficiency anemia. Forty percent of patients with low MCV had etiology of anemia other than iron deficiency. Among the patients with macrocytosis 87.5% had B12/folate deficiency and 12.5% had zidovudine induced anemia. Thirteen percent had low vitamin B12 levels. However only 50% percent of patients with low B12 levels had macrocytosis.

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