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Original Research Article

Study of aetiology of anemia in HIV positive individuals

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ABSTRACT

Background: HIV/AIDS is a global pandemic. As of 2014, approximately 37 million people have HIV worldwide with the number of new infections that year being about 2 million. This is down from 3.1 million new infections in 2001. The objective of the study was to study the immunological status as indicated by the CD4 count and aetiology of anemia in HIV positive individuals.
Methods: This study was carried out on 100 consecutive HIV patients in the Department of Medicine, Vijayanagara Institute of Medical Sciences Bellary, Karnataka during the period from October 2014 to May 2016.
Results: In this study, 100 patients with HIV infection and anemia were studied to find the etiology of anemia in HIV positive patients Only patients with Hb less than 10 g/dl (moderate to severe grade) were included in this study. 42% patient had moderate grade anemia and 58% had severe grade anemia patient mild grade anemia was excluded. 13 patient had their MCV <76 fl. 60 patient had their MCV between 76-96 fl and 27% had their MCV of >96 fl. 54% of patient had anemia due to chronic disease.
Conclusions: 54% of patient had anemia due to chronic disease, 12% had iron deficiency anemia, 11% had anemia due to vitamin B12 deficiency, 22 % had anemia due to zidovudine induced anemia and 1 patient had anemia due hemolysis.

Keywords: HIV positive, CD4 count, Anemia, MCV, Iron deficiency anemia

INTRODUCTION

Without treatment, average survival time after infection with HIV is estimated to be 9 to 11 years, depending on the HIV subtype.[1] AIDS was first clinically observed in 1981 in the United States. The initial cases were a cluster of injection drug users and gay men with no known cause of impaired immunity who showed symptoms of pneumocystis carinii pneumonia (PCP), a rare opportunistic infection that was known to occur in people with very compromised immune systems. Soon thereafter, additional gay men developed a previously rare skin cancer called Kaposi's sarcoma (KS). Many more cases of PCP and KS emerged, alerting U.S. Center for Disease Control and Prevention (CDC) and a CDC task force was formed to monitor the outbreak. The earliest retrospectively described case of AIDS is believed to have been in Norway beginning in 1966.

Anemia in human immunodeficiency virus (HIV)–infected patients can have serious implications, which vary from functional and quality-of-life decrements to an association with disease progression and decreased survival. In 2002, 16 members of the Anemia in HIV Working Group, an expert panel of physicians involved in the care of HIV-infected patients that met first in 1998, reconvened to assess new data and to translate these data into evidence-based treatment guidelines. The group reached consensus on the prevalence of anemia in the highly active antiretroviral therapy era; the risk factors that are independently associated with the development of anemia; the impact of anemia on quality of life, physical

functioning, and survival; the impact of the treatment of hepatitis C virus co infection on anemia in HIV-infected patients; evidence-based guidelines for treatment of anemia in HIV-infected patients, including the therapeutic role of Epoetin Alfa; and directions for future research.[2]

The overall incidence of anemia among HIV positive patients ranges from 10% in asymptomatic patients up to 92% in individuals with full blown AIDS.[3] In HIV positive patient's anemia is a prognostic marker of future disease progression or death, independent of CD4 and viral load.[3] Anemia impacts a range of dimensions of quality of life. The common causes of anemia in HIV and non HIV patients are varied so treatment will differ. So the present study was conducted to find out the immunological status and aetiology of anemia in HIV positive individuals.

METHODS

A study was carried out on 100 consecutive HIV patients in different stages of disease attending the Department of Medicine, Vijayanagara Institute of Medical Sciences Bellary, Karnataka. Study period was 18 months from October 2014 to May 2016. All respondents were adults, aged more than 18 years.

HIV patients above 18 years of age and anemia with hemoglobin less than 10 gm/dl were included in the study. HIV patients below 18 years of age and HIV patients who do not give consent for the study were excluded from the study. Informed consent was taken prior to inclusion in the study. A detailed and careful history will be taken regarding the duration and symptoms of the disease. A thorough systemic examination will be done.

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. Further work up for anemia including peripheral smear examination, mean corpuscular volume estimation, serum ferritin and B12 levels were done. Bone marrow aspiration and biopsy was done for few of the patients as part of anemia evaluation. Other tests were done as per the needs of the patient.

Descriptive Analysis was done using percentages, proportions, mean and standard deviations and inferential analysis was done using unpaired T-tests, chi-square.

RESULTS

100 patients with HIV infection and anemia were included in the study. In our study 12 patients were between 18-30 years, 39 patients were between 31-40 years of age, 43 patients were 41-50years of age and 6 patients were >50 years. Minimum age was 18 years and maximum mage was 55 years (Mean ag was 39). Out of 100 HIV patients 72 were male and 28 were female. Among 72 male patients 47 patient having CD4 count of <200 and 25 were having CD4 >200. Among 28 female patients 15 patient having CD4 count of <200 and 13 were having CD4 >200.

Table 1: Duration since diagnosis.

Duration of disease	Number of patients <200		Number of patients >200		Total
Up to one month	8	44.4%	10	55.6%	18
1-12 months	28	64%	19	36%	47
>12 months	25	58%	13	42%	38
Total	61	58%	39	42%	100%

Chi square= 3.714, p=0.1556 not significant

Table 2: MCV levels.

MCV	Number of patients	%
<76 fl	13	13
76-96 fl	60	60
>96 fl	27	27
Total	100	100

Among 18 patients 8 having CD4 count of <200 and 10 were having CD4 >200 with disease duration >1 month. Among 44 male patients 28 having CD4 count of <200 and 16 were havingCD4 >200 with disease duration 1-12 months. Among 38 male patients 25 having CD4 count of <200 and 13 were havingCD4 >200 with disease duration >12 months. (Table 1)

Table 3: CD 4 count and anemia due to chronic disease and anemia due to other cause.

	CD4 <200	CD>200	Total
Anemia due to chronic disease	41	13	54
Anemia due to other cause	20	26	46
Total	61	39	10

Out of 100 HIV patients 61 were having cd-4 counts of <200//µl, mean haemoglobin was 6.2 39were having cd-4 counts of >200//µl, mean haemoglobin was 6.7.

Only patient below Hb 10 mg/dl was included in the study, out of which 58 had severe anemia and 42 had moderate anemia. Out of 100 patients, 13 % patients had MCV OF >76 fl, 57% patients had MCV between 76-96 fl, 27% patients had MCV >96 fl. Out of 13 pt with MCV <76 fl, 9 pt had iron deficiency anemia. Out of 27 pt who had MCV of >96, 11 pt had vitamin B12 deficiency with macrocytosis. (Table 2)

Out of 100 patient, 69 had normocytic anemia, 14 had megaloblastic and 17 had microcytic anemia. HIV induced

anemia (anemia of chronic disease) is characterized by normocytic and normochromic red cells and an inappropriately low reticulocyte response. This is reflected by a low serum iron, serum ferritin values increase threefold over basal levels in the face of inflammation and a hypoproliferative marrow. (Figure 1)

Iron deficiency anemia is characterized by microcytic and hypochromic anemia and is reflected by low serum iron, low mcv and low ferritin. B12 deficiency anemia is characterized by macrocytic anemia and is reflected by low vitamin B12 and high MCV.

Zidovudine induced anemia can be identified by features: patient on zidovudine, macrocytic/normocytic anemia.

Improvement in hemoglobin by greater than 2 three months after stopping zidovudine Among patients with low immunological status as expressed by CD4 count less than 200/µl, the etiologies of anemia were Anemia of chronic disease (67%), zidovudine induced anemia (15%) B12/folate deficiency (11.5%) Iron deficiency (6.5%). Among patients with CD4 count greater than 200/µl, the most common etiologies of anemia were anemia of chronic disease (33.5%) zidovudine induced anemia (33.5) iron deficiency (20%) B12/folate deficiency (10%) anemia secondary to hemolysis (2.5). (Table 3, Figure 2)

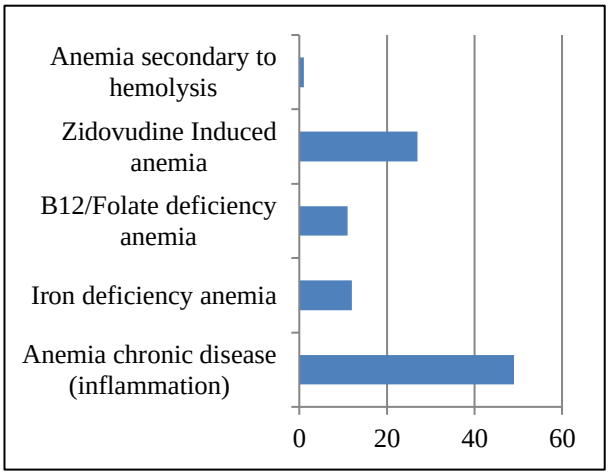

Figure 1: Etiology of anemia.

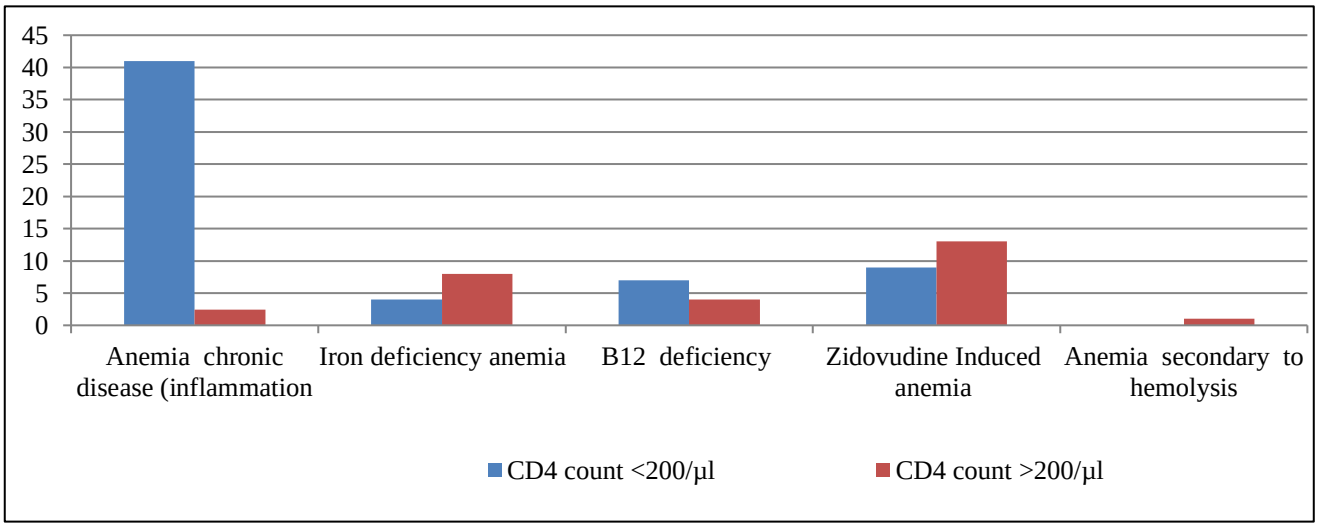

Figure 2: CD4 count and etiology of anemia.

DISCUSSION

Minimum age of the subjects was 18 years and the maximum age was 51 years with mean age of 39 years. These demographic data are similar to those documented in other studies done in India.[4]

In our study 72% had established diagnosed greater than 1 year and 38% has diagnosed within 1 years, this was much similar to many studies.[4] The mean CD4 count was 237/µl. Mean CD4 count in males was 233/µl and in females was 229/µl. 62% of patients had CD4 count lesser than 200/µl in and 39% of the patients had greater than 200/µl. These features were similar to the other studies done in South India.[4] Thus, the patients included in this study had advanced disease. Severity of anemia was classified according WHO grading.[5] 58% percent had severe gradeanemia, 42% had moderate grade. This was in contrast to a study done by Meidani et al in which majority of patients were found to have mild to moderate grade anemia occurring in 67% of patients.[6] This is probably because our study was done in a tertiary care hospital and majority of the patients had advanced disease and severe grades of anemia.

In our study 60% percent had their MCV in normal range. 13% percent had MCV less than 76 fl and 27 had MCV greater than 96 fl. This is not similar to the study done by Tripathi et al which showed normal MCV in 88.5%, low MCV in 6.56% and high MCV in 4.92% of patients.[7] This

is probably because 40% of patient were on zidovudine, and it has shown in study done KIM et al.[8] That MCV value increase in HIV infected patient under zidovudine. 77% of patients with MCV >76 fl had iron deficiency anemia and 33% of patient with low MCV had etiology of anemia other than iron deficiency anemia.

Among 27 patient with MCV of >96 fl, ten patient had vitamin B12 dificiency. High MCV values are seen in patient on zidovudin. Seventeen out of fourty patient had MCV of >96.This was similar to the study done by Romanelli et al showed that twenty-seven of the 41 patients for whom zidovudine-containing antiretroviral regimens was prescribed developed macrocytosis (65.8%).[9] Mugisha et al concluded that 12-weekly MCV measurements may be useful in monitoring adherence to AZT-containing regimens.[10]

In our study 11% had low vitamin B12 levels. According to Remaca et al Low vitamin B12 levels (B12) are often observed in patients infected with human immunodeficiency virus in 18% of patients.[11] In a study by Balt, J Assoc Nurses AIDS Care Prevalence of B12 deficiency in persons with HIV infection has been shown to be Significant.[12] In a study by Rule SA et al Am J Hematol shown that subnormal serum B12 levels are common in HIV disease and occur at an early stage.[13]

In our study 11% of patient had low vitamin B12 level and was not significant (0.062) and fall of CD4 in comparison with vitamin B12 also was not significant (p-0.849). Patients with low B12 concentration was not correlating with macrocytosis in HIV patient was shown by Burkes et al.[14,15] In our study only 90% percentage of patients with low B12 levels had MCV >96 and in most cases the cause of low vitamin b12 is unknown and may reflect a serum abnormality.

In a study by Lopez-Caldero et al in 2015 high ferritin levels are not uncommon in HIV patients, and they correlate with immunosuppression defined as CD4 count <350 cells/µL.[16] In our study most of the patient had high serum ferritin a positive phase reactant.

In our study most of patients had anemia of chronic disease in comparison to other etiologies. 54% had anemia of chronic disease, 22% had anemia secondary to use of zidovudine,12% had iron deficiency anemia, 11% had B12/folate deficiency and 1% had anemia due to hemolysis.

Levin et al, Sullivan et al, Macroft et al have shown that low CD4 cell counts(<200 cells/µl) and higher HIV-1 RNA level in plasma have been independently associated with anemia and also a study by Christian et al done in Ghana hemoglobin can used as a surrogate marker for CD4 count for monitoring of disease progression and is explained that disease progression can be associated with cytokine mediated Myelosupression.[17] 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 CD4 and anemia if all the aetiologies of anemia are included as in our study.

In our study there was significant difference in hemoglobin values among patients who had CD4 count less than 200/µl (mean Hb 6.387gm/dl and CD4 count greater than 200/µl (mean Hb 7.469gm/dl) (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 (67%), zidovudine induced anemia (15%), B12/folate deficiency (11.5%), iron deficiency (6.5%).

Among patients with CD4 count greater than 200/µl, the most common etiologies of anemia were anemia of chronic disease (33.5%), zidovudine induced anemia (33.5) Iron deficiency (20%), B12/folate deficiency (10%), anemia secondary to hemolysis (2.5%). In patients who had anemia of chronic disease mean Hb(6.554gm/dl) in patient with CD4 >200/µl and disease mean Hb(7.785gm/dl) in patient with CD4 <200/µl which was significant with p value of 0.0023.

Patient with HIV are prone to develop anemia due to many causes like progressive disease, opportunistic infections and bone marrow infiltration and it is difficult interpret this as a specific side effect. Moreover, HIV patient are on multiple drugs and difficult to determine effect of single drug. A study Moinuuddin et al showed that more 20% of cases of anemia was associated in HIV is drug induced and in our study 22%of patient had drug induced anemia.[6,7,18] In our study there was significant difference mean Hb of patient on ART (Hb-6.09 gm/dl) and mean Hb of patient not on ART (Hb-7.41gm/dl) (P-0.001). However, patient on ART had more advanced disease and duration of illness been also more in patient on ART than with patient not on ART. By the fact that progressive disease, opportunistic infections is more in advanced Disease of HIV so ART causing anemia cannot be interpreted precisely.

In a study by Agarwal et al done in Varanasi 16.2% patients developed ZDV induced anemia in a prospective study in which patients were followed up over a period of 1 year. In our study there was significant difference in the hemoglobin levels in patients on zidovudine (6.09gm/dl) and non-zidovudine regimens (7.41gm/dl) (p=0.0011). many patients developed anaemia with 4-5 month of start of zidovudine which is similar to many studies. In most patients there was recovery within a month after switching on to another therapy.

In our study we found that mean haemoglobin was significant lower in established cases than in the newly diagnosed case. Probably as newly diagnosed case are not in advanced state of disease. In well-established case

progressive disease, opportunistic infections and drug induced anemia also contribute to the disease.

CONCLUSION

In this study, 100 patients with HIV infection and anemia were studied to find the aetiology of anemia in HIV positive patients the patients included in this study had advanced disease. Out of 100 patients 42% patient had moderate grade anemia and 58% had severe grade anemia patient with mild grade anemia was not included in the study. Most of the patient had anemia of chronic disease when compared to other etiology. 54% of patient had anemia due to chronic disease, 12% had iron deficiency anemia, 11% had anemia due to vitamin B12 deficiency, 22 % had anemia due to zidovudine induced anemia and 1patient had anemia due hemolysis. Mean haemoglobin in patient on ziduvudine was 6.092 and patient on other than zidovudine was 7.469.

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