Review Article

HEMATOLOGICAL MANIFESTATIONS IN HIV-INFECTED PERSONS: Literature Review

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AIDS (Acquired Immune Deficiency Syndrome) is the most serious of all infectious diseases known to Man. Since its discovery in 1981, the disease has attracted attention from health care professionals around the globe. The disease is now viewed as a threat to social and economic fabric of the world community. Currently 30-40 million people are infected with HIV; most of them are in Sub-Saharan Africa and South East Asia. Serious apprehensions about the problem and effective preventive measures have reduced its prevalence in the developed countries. Despite a global awareness and prevention campaign, one person still dies of HIV every 3 minutes around the world.

Whereas infection with HIV is a multi-system disease, hematological abnormalities are amongst the commonest clinicopathological manifestations of AIDS. Pathogenesis of these changes is multi-factorial and includes direct invasion by the virus, sequelae of HIV-related infections; HIV-associated malignancies and drugs.

This article is a systematic review of some of the better known hematological manifestations in HIV-infection. It also includes an analysis of their reported incidence in the world literature. Sources of informations in this article are electronic database as well as the published material.

NORMAL HEMATOPOIESIS

Pluripotential hematopoietic stem cells in the bone marrow are the basic units of hematopoiesis and possess dual ability to replicate and also to differentiate into committed progenitors i.e. CFU-GEMM (Colony Forming Unit-granulocytes, erythrocytes, monocytes and macrophages). CFU-GEMM, under the influence of various cytokines like GM-CSF, erythropoietin, and thrombopoietin gives rise to more committed progenitors. These colony-forming units eventually generate the mature forms like granulocytes, monocytes, erythrocytes and platelets respectively. This is shown in (Fig. 1)

In addition to the role of stem cells and the hematopoietic factors in hematopoiesis, importance of bone marrow microenvironments has recently been appreciated. Bone marrow microenvironments include T-lymphocytes, macrophages, endothelial cells and fibroblasts. They produce a host of factors that stimulate normal hematopoietic cell lines. These are listed in Table-I.

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Table-I: Growth factors produced by the microenvironments of the marrow

Microenvironment	*Growth factors*	*Functions*
T lymphocytes	Stem cell factor	Early activation of stem cells
	Plt3 ligand	Early initiation of growth of all cell types
	Pan-growth factor	Early marrow progenitor cell stimulation
	IL-3	Late stage of differentiation
Macrophages	TNF and IL-1	Act on fibroblasts and endothelial cells
Fibroblasts and endothelial cells	GM-CSF	G-CSF production M-CSF production

I. ANEMIA IN HIV INFECTION

Incidence:

Anemia is a frequent complication of HIV infection. Review of a study of HIV disease in 1989 showed that 18% of all HIV-sero-positive patients had anemia. Incidence of anemia in middle stage HIV disease and in CDC-defined AIDS was 50% and 75% respectively[1]. A multicenter AIDS cohort study concluded that 3.2% of HIV sero-positive individuals with mean CD_4 cell count of greater than 700/ml were anemic while anemia was present in 20.9% of those with CD_4 count less than 249/ml[2]. This variation in the incidence of anemia, at different stages of HIV disease is due to a number of factors; some of these are:

- CD_4 cell count
- Chemotherapy
- Race / Ethnicity
- Concurrent illness
- Clinical disease status

Besides an increase in the incidence of anemia in HIV-infected patients, its association with increased morbidity and mortality in AIDS is also well recognized. In 1994 a multicenter AIDS cohort study in USA showed that reduced "hemoglobin level was predictive of decreased survival independent of CD_4 cell count"[3]. A study from John Hopkins School of Medicine showed that treating severe anemia especially with erythropoietin reduced the risk of early death in HIV infected anemic patients[4].

In January 1998 a large epidemiological study on the effect of anemia in HIV-infected patients was published by the Division of HIV / AIDS, Center for Disease Control and Prevention. More than 32000 HIV-infected patients who received treatment in various hospitals in USA from January 1990 to August 1996 were analyzed. The report indicates that 28% of men and 31% of women with asymptomatic HIV infection were anemic (Hb < 14 and < 12 g/dl respectively). The figure rose to 87% and 77% respectively for patients with clinically manifest AIDS[5]. The study highlighted four important aspects of anemia in HIV infection (Table-II).

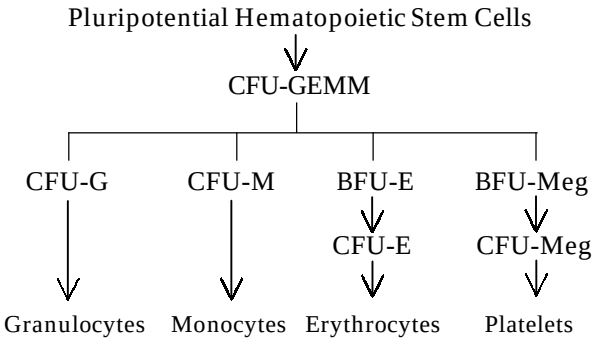

Fig 1: Normal hematopoiesis (BFU-E: Burst forming unit-erythrocytes, BFU-Meg: Burst forming unit-megakaryocytes)

*Table-II:*One year incidence of anemia in HIV / AIDS

Clinical status of HIV-AIDS	*No. of patients*	*Incidence of anemia*
HIV infection but no AIDS	6094	3.2 %
Immunological AIDS (CD_4 < 200/µl)	2579	12.1 %
Clinical AIDS	4642	36.9 %

Median survival:

Median survival was significantly shorter for patients with anemia than for those without anemia, regardless of the CD_4 cell count at the time of initial diagnosis.

Effect of CD_4 cell count on mortality:

Mortality rate associated with anemia was influenced by CD_4 cell count at the time of diagnosis of anemia. For a comparable level of hemoglobin the mortality was 148% higher in patients with CD_4 count less than 200/ul; the risk was only 56% greater if CD_4 cell count at the time of presentation was greater than 200/ul.

Effect of resolution of anemia:

Risk of fatal outcome was 170% greater in persons who did not respond to treatment for anemia as compared to those who did.

Pathogenesis of anemia:

Anemia in HIV infection is multifactorial; some of the causative mechanisms are:

- Anemia of chronic disease
- HIV-related infections
- Hemolysis
- Drug toxicity
- Malignant myelo infiltration
- Gastrointestinal bleeding
- Vitamin B_{12} deficiency
- Hypogonadism
- Anemia of chronic diseases:

This is the most frequent cause of anemia in HIV-infected patients. Red cells are mostly normocytic and normochromic; there may be mild anisocytosis with a few microcytes. Primary defect is the failure of the bone marrow to produce normal number of erythrocytes (hypoplastic anemia). Some of the postulated mechanisms are:

a) Direct toxic effect of HIV on hematopoietic stem cells and bone marrow microenvironment
b) Abnormal expression of inhibitory cytokines.
c) Relative deficiency of erythropoietin
d) Defective iron metabolism and reutilization.

Recent studies suggest that there may be a direct cytotoxic effect of HIV on hematopoietic stem cells as well as on stromal microenvironments of the bone marrow. This leads to decreased production of G-CSF and IL-3 resulting in defective erythropoiesis (table-1).

Inhibitory effect of increased activity of IL-1, TNF-a and IFN-gon bone marrow erythropoiesis has also been postulated as a contributory factor towards marrow hypoplasia. There is good evidence that serum concentration of endogenous IFN-gcorrelates inversely with the hemoglobin level in patients with HIV infection[6]. Secretion of these cytokines is most likely triggered by the underlying chronic inflammation.

Other important mechanisms of anemia in AIDS are decreased erythropoietin production as well as decreased responsiveness of stem cells to erythropoietin. Though serum levels of erythropoietin were elevated in HIV-infected persons with anemia, the increase was less than that seen in the HIV sero-negative patients with anemia of the same severity[7].

Iron deficiency is also well documented in patients with AIDS. Clinical guidelines published in 2002 indicate that 50% of children with HIV infection have low serum iron[8]. Difficulty lies in distinguishing true iron deficiency anemia from anemia of chronic disease with low serum iron. Increased iron in the bone marrow macrophages, high serum ferritin and low total iron binding capacity rule out iron deficiency anemia. Serum ferritin is not a reliable indicator of iron deficiency in HIV-infected persons. This is because serum ferritin, being a marker of acute and chronic inflammation, is almost always increased in AIDS. Iron deficiency in AIDS has also been linked to intestinal malabsorption as well as poor intake of iron. Chronic gastrointestinal infections may also contribute to malabsorption of iron in patients with AIDS.

HIV-related infections:

A number of opportunistic infections can lead to defective hematopoiesis in HIV-infected patients; the commonest being Parvovirus B_{19} and Mycobacterium avium complex (MAC). About 64% of HIV-infected patients have antibodies against Parvovirus B_{19} though the incidence of clinical disease is considerably less. Parvovirus is a small non-enveloped DNA virus that causes erythema infectiosum (Fifth disease) in children and transient aplasia in patients with hereditary spherocytosis and hemoglobinopathies. The classical picture of erythema infectiosum is usually absent. Persistent infection results from an inability to mount an adequate antibody response causing pure red cell aplasia.

B_{19} infection should always be considered in patients with AIDS associated anemia when more common causes of anemia are not readily apparent. Bone marrow typically shows giant pronormoblasts with clumped basophilic chromatin and clear cytoplasmic vacuoles. Diagnosis is established through B_{19} DNA dot blot hybridization of the serum. Association of anemia with Parvovirus B_{19} infection is also supported by the fact that anemia resolves on treating infection with IV immunoglobulins for 5-10 days.

In a study that was conducted in 1986, mycobacterium avium complex (MAC) infection was diagnosed in 18% of patients with HIV disease during the course of their illness[9]. The microorganism causes widespread infection. Bone marrow is also affected resulting in moderately severe anemia; in some cases pancytopenia is produced. Although the exact mechanism of anemia is not known, there is evidence that cytokine-induced bone marrow suppression is the cause of anemia. Despite clear association of MAC with anemia, it is yet to be known if anti-mycobacterial therapy can improve the hematological status.

Other less common infectious causes of anemia in HIV-infected patients include tuberculosis, histoplasmosis, cryptococcosis, and pneumocystis carinii.

Hemolytic anemia:

Hemolysis as the sole cause of anemia in AIDS is uncommon. It may develop as a consequence of

- G6PD deficiency
- Hemophagocytic syndrome
- Auto-antibodies against RBCs
- Thrombotic thrombocytopenic purpura
- Coincident Hepatitis B and C infections.
- Hypersplenism due to advanced liver disease

Direct antiglobulin (Coomb's) test is positive in 37% of HIV-infected persons[10] but clinically significant hemolysis is rare. This indicates that positive Coomb's test in HIV-infection may simply be a reflection of polyclonal hypergammaglobulinemia which is common in HIV infection. Thrombotic thrombocytopenic purpura (TTP) is also reported in HIV-AIDS patients. Hemolysis can also occur in HIV infected patients receiving drugs like Trimethoprim-sulfamethoxazole and Dapsone, particularly in G6PD deficiency.

Drug-induced anemia:

More than 20% of cases of anemia associated with HIV are drug induced. The commonest agents are Zidovudine (AZT), and trimethoprim sulphamethoxazole. AZT causes significant macrocytosis (MCV > 100 fl), which is now being used by many as a screen for patient's compliance with therapy. Clinically significant anemia has been observed in as many as 34% of patients after 6 weeks of therapy while 31% of patients develop severe anemia that requires red cell transfusion, while receiving the drug. Stage of illness is directly proportional to the severity of anemia; only 1% of asymptomatic individuals develop significant reduction in Hb[11].

Anemia with AZT is dose related and is less commonly seen in patients on low dose therapy though a number of cases due to idiosyncracy to AZT have also been reported. Suspected cause of anemia is bone marrow suppression but the actual mechanism is not clear. It is

important to note that not all antiretroviral drugs cause anemia; one example is Stavudine which is associated with macrocytosis but it does not cause anemia.

Treatment of anemia associated with trimethoprim-sulphamethoxazole which is used for the pneumocystis carinii infection in AIDS is due to folate deficiency and is more prevalent in patients with poor nutritional status. Dapsone on the other hand leads to generalized myelosuppression besides causing hemolytic anemia[12].

Less common causes of anemia:

Gastrointestinal involvement in AIDS may cause blood loss anemia. Infections like cytomegalovirus colitis and malignancies like Kaposi's sarcoma may also cause significant anemia due to gastrointestinal blood loss. Infiltration of the bone marrow by AIDS-associated lymphoma is less frequent but it can cause severe anemia.

Hypogonadism is relatively common in HIV-infected men. The associated signs may include pallor and fatigue with reduced hemoglobin levels. Estimation of serum testosterone level is recommended if anemia is associated with other signs of hypogonadism[13].

II. THROMBOCYTOPENIA IN HIV INFECTION:

Association of HIV-infection with thrombocytopenia was recognized long ago. In 1984, a physicians' handbook listed thrombocytopenia along with fever, weight loss, fatigue and swollen lymph glands as a signal that a patient might have AIDS[14].

Incidence:

Thrombocytopenia is believed to be present in as many as 40% of HIV-infected persons. In approximately 10% of the patients, it may be the first sign of AIDS[15]. In a multicenter AIDS cohort study among 1500 HIV positive individuals, 6.7% had platelet count of less than 150,000 ml on at least one semiannual visit[16]. A study conducted in HIV-infected children in 1986, revealed that 20 to 30% of patients develop thrombocytopenia at some stage during the course of the illness.

In a center for disease control study in 1996[17], one year incidence of thrombocytopenia (platelet count < 50,000 / ml) in HIV-infection was 8.7% in clinical AIDS, 3.1% in immunological AIDS (CD_4 cell count < 249/ml) and 1.7% in non-clinical, non-immunological HIV-infection (CD_4 cell count > 700/ml).

Pathophysiology and clinical course:

HIV-related thrombocytopenia though often asymptomatic; may present with petechiae, ecchymosis, epistaxis, menorrhagia, gingival bleeding and bleeding in the gastrointestinal tract and in the CNS. According to a study conducted in 1992, thrombocytopenia in AIDS can be divided into four clinical subsets. Of the 52 HIV-infected thrombocytopenic patients it was noted that 17% had acute ITP-like illness, 40% had chronic ITP-like disease, while 35% and 8% of patients had splenic sequestration type and hypoplastic thrombocytopenia respectively. Hence thrombocytopenia in HIV infection may be the result of defective hematopoiesis but in many instances it is a relatively isolated hematological abnormality related to increased platelet destruction.

Some important mechanisms of HIV-associated thrombocytopenia are:

- Immune thrombocytopenic purpura (HIV-ITP)
- Thrombotic thrombocytopenic purpura
- Defective thrombopoiesis
- Drug-induced thrombocytopenia
- HIV-related infections

Immune thrombocytopenic purpura (HIV-ITP):

Immune thrombocytopenia is the commonest cause of thrombocytopenia in general population and is due to increased platelet destruction caused by the antibodies against platelet

receptors like IIb and IIIa. In HIV-related ITP a similar mechanism is operative. Marked increase in the platelet associated IgG, IgM, C3 and C4 levels have been demonstrated in the blood of HIV-infected persons. Cross reactive antibodies between HIV gp 160/120 and platelet gp IIb/IIIa have been found. It is however important to note that platelet antibodies are not helpful in establishing the diagnosis of immune mediated thrombocytopenia as there is a high false positive and false negative rate. Instead, response to treatment with intravenous immunoglobulins (IVIg) and to IV anti-D is regarded as a more reliable diagnostic tool in HIV-ITP.

Defective thrombopoiesis:

Reduced platelet production in the bone marrow in HIV infection is thought to be due to direct suppression of megakaryocytes by the virus. Megakaryocytes express both CD_4 and CCR_5 receptors which enable them to engulf HIV particles. Ratner *et al* discovered a distinct amino acid sequence in HIV infected thrombocytopenic patients which was not present in non-thrombocytopenic HIV-infected persons[18]. They postulated that HIV strains capable of infecting T cells and macrophages in the bone marrow may be responsible for thrombocytopenia in AIDS. The observation that antiretroviral therapy like zidovudine increases platelet count is also consistent with the belief that direct damage to the megakaryocytes by HIV has an important role to play in HIV-related thrombocytopenia.

Drug-induced thrombocytopenia:

The two most frequently used drugs in the treatment of HIV-infection that have significant association with thrombocytopenia are Gancyclovir and Pentamidine. Gancyclovir is an acyclovir analog that is effective against cytomegalovirus infection in AIDS. It is associated with severe dose dependant cytopenias including thrombocytopenia. This adverse effect is enhanced when the drugs is used in combination with AZT. Pentamidine is used for the treatment of pneumocystis carinii infection in AIDS. Another important pharmacological agent that causes thrombocytopenia is trimethoprim-sulphamethoxazole.

HIV-related infections:

Opportunistic infections with histoplasma and cryptococcosus can also produce thrombocytopenia in HIV-infected persons. Also any neoplastic condition that involves the bone marrow can lead to thrombocytopenia. In addition, HIV-infected persons are also prone to develop thrombocytopenia for reasons unrelated to their HIV infection. These include alcohol ingestion, splenomegaly and liver disease.

III. NEUTROPENIA IN HIV-INFECTION:

Neutropenia is common in HIV-infected persons. A study in 1988 showed that 13% of patients with asymptomatic HIV-infection had neutropenia while the incidence rose to 44% in clinical AIDS[19]. Some researchers believe that as many as 50% of patients develop neutropenia in advanced HIV disease. The multicenter AIDS cohort study conducted in 1987 found that neutropenia was especially common in patients with more profound immunodeficiency. Taking into account patients' CD_4 cell count, it was shown that the incidence of neutropenia was 0.8% in HIV-positive patients with CD_4 count > 700 cells/ml; it rose to 13.4% in those with CD_4 count < 249 cells/ml.

Neutropenia and risk of infection in AIDS:

In a study that was carried out in 1997, it was suggested that there was a strong correlation between the level of absolute neutrophil count (ANC) and the need for hospitalization for bacterial infections[20]. In a detailed study in 62 HIV-infected patients, 24% with ANC below 1000/ml developed infectious complications within 24 hours of the onset of neutropenia[21]. It is postulated that there is a 2-3 fold increased risk of bacterial infections in

HIV-infected patients with ANC < 1000 cells/ml; the risk increases by 7 to 9 times when the count falls below 500 cells/ml[22]. Other factors positively associated with increased risk of infections in neutropenic AIDS patients are the presence of a central venous line, recent history of neutropenia and low CD_4 count. Many studies have confirmed a similar relationship between the neutrophil count and the risk of bacterial infections in AIDS.

Etiology and pathogenesis:

Most of the drugs cause direct bone marrow suppression. An autoimmune mechanism involving antibodies against white blood cells has also been suggested but studies have shown that anti-granulocyte antibodies are not related to the increased incidence of neutropenia in HIV-infected persons[23]. Other proposed mechanisms are decreased growth of progenitor cells CFU-GM and decreased serum levels of granulocyte colony stimulating factor (G-CSF)[24].

In addition to neutropenia defective granulocytic functions have also been documented in HIV infection contributing to defective phagocytosis. It is however widely believed that these findings are not of much clinical significance[25]. Some of the important causes of neutropenia in HIV-setting are:

1. Drug toxicity
2. HIV-related infections
3. Nutritional deficiencies
4. Autoimmune destruction
5. Malignant infiltration of the bone marrow

Wide range of drugs in AIDS can cause leukopenia (Table-III). This is usually dose dependent though it has also been reported as an idiosyncratic phenomenon.

Zidovudine (AZT) is the commonest pharmacologic agent which is responsible for neutropenia in patients with HIV disease. A double-blind placebo-controlled trial in patients with moderate to advanced HIV disease, published in New England Journal of Medicine in 1987, showed that 16% of AZT-treated patients developed severe neutropenia (<500 cells/ml) compared to only 2% in placebo-treated group. Neutropenia due to AZT therapy is dose-related; reduction in the dose or withdrawal of the drug leads to a prompt rise in the neutrophil count. For this reason, AZT-induced neutropenia is not often associated with an increased risk of bacterial infections provided the drug is discontinued when the count falls below 1000 cells/ml.

Chemotherapy for the treatment of AIDS-related malignancies like Kaposi's sarcoma and non-Hodgkin's lymphoma is also a cause of neutropenia in these patients. In a study surveying a group of patients with Kaposi's sarcoma treated with ABV regime (adriamycin, bleomycin and vincristine), one third of the patients developed significant neutropenia; (neutrophil count < 1000ml)[26]. The incidence of bacterial infections is however the same as in patients without HIV infection receiving cancer chemotherapy.

Gancyclovir which is used for treating HIV-related CMV infection causes significant neutropenia. Serious infectious complications are rare due to the prompt recovery following discontinuation of the drug[27]. Pentamidine and trimethoprim-sulfamethoxazole (TMP-SMX) used for the treatment of Pneumocystis carinii pneumonia also cause neutropenia but secondary bacterial infections are distinctly uncommon. Other notable drugs causing neutropenia in AIDS patients are listed in table-III.

Table-III: Drugs causing neutropenia in HIV-infected persons

Class	*Drugs*
Anti retroviral	Zidovudine, Lamivudine, Stavudine
Anti viral	Gancyclovir, Foscarnet
Antineoplastic	Methotrexate, Vinblastine, Doxorubicin, Cyclophosphamide, Daunorubicin
Antifungal	Amphotericin, Flucytosine
Antimicrobials	Sulfonamides, Pyrimethamine, Trimethoprim
Immune modulators	Interferon-a

IV. COAGULATION ABNORMALITIES IN HIV-INFECTION:

Coagulation abnormalities in the setting of HIV-infection are not common though an increased risk of venous thromboses is well established. In a CDC study it was found that the over all incidence of thrombotic episodes were 2.6 per 1000 HIV-infected persons[28]. Important factors responsible are old age; opportunistic infections; immobility; and drugs (like megesterol acetate and indinavir). Protein S deficiency, anticardiolipin antibodies and heparin cofactor II deficiency have also been regarded as possible etiological factors in predisposition to thrombosis.

Lupus anticoagulants and anticardiolipin antibodies are present in the sera of 43% and 47% of HIV-infected individuals respectively[29,30]. Though these antibodies are commonly associated with thrombocytopenia and hypoprothrombinemia, the incidence of clinically manifest coagulation abnormalities is low. Frequency of thrombotic manifestations in antiphospholipid antibody-positive HIV-infected patients is low as compared to patients with antibodies positive systemic lupus erythematosus. Prolongation of APTT is an indicator that these patients have anticardiolipin antibodies.

In 1993, it was noted that 31-76 % of HIV-infected individuals had deficiency of protein S[31]. Its exact cause is not known but anti protein S antibodies have been regarded as a possible mechanism. Significance of protein S deficiency in the pathogenesis of thromboembolism, though highly suggestive, is yet to be proven. An alternate explanation is that the development of these antibodies is merely a reflection of the polyclonal increase in serum immunoglobins in these patients.

Hematological abnormalities are a frequent accompaniment of HIV-AIDS. In view of the high incidence of hematological disorders in clinically silent HIV infection, it is strongly recommended that in all cases of unexplained blood dyscrasias the possibility of 'silent' HIV infection must be seriously entertained and appropriate investigations must be done to clarify the status of HIV-infection.

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