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Review Article

ANAEMIA IN HIV

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Abstract: Anaemia in HIV-infected individuals, still a common hematologic complication in the highly active antiretroviral therapy (HAART) era, is associated with shortened survival, increases in the rate of disease progression, and reduction in quality of life. There are limited data on anemia in HIV-infected patients. A recent study showed that, increasing numbers of women with AIDS are from rural and smaller metropolitan areas rather than large urban centers, communities that often face additional barriers to access and retention. In Conclusion, this review will cover the area of etiology, guidelines for the assessment, diagnosis, monitoring, and treatment of anemia in patients with HIV/AIDS which in turn will help to improve clinical practices in diagnosis and treatment of anaemia in HIV. This will increase awareness of the prevalence of anemia in HIV-infected patients and its impact on their lives. It will enhance the screening for anemia and the adaptation of a proposed classification system of anemia based on a graded decrease in hemoglobin levels.

Keywords: HIV, Immunity, Anaemia.

INTRODUCTION

Anemia is common condition in HIV infection, particularly in advanced disease states. Anaemia is a frequent complication of infection with the human immunodeficiency virus (HIV) and may have multiple causes. In different study settings, the prevalence of anemia in persons with acquired immunodeficiency syndrome (AIDS) has been estimated to be 63% to 95%, (Groopman, 1990) making it more common than thrombocytopenia or leukopenia in patients with AIDS (Calenda & Chermann, 2009).This high prevalence of anemia may be because of a high incidence of anemia, a long duration of anemia, or a combination of both.

HIV infection may lead to anemia in many ways: changes in cytokine production with subsequent effects on hematopoiesis (Maciejewski *et al.*, 1994); decreased erythropoietin concentrations (Camacho *et al.*, 1992); opportunistic infectious agents such as Mycobacterium aviumcomplex (Horsburgh, 1991) and parvovirus B-19 (Naides *et al.*, 1993); administration of chemotherapeutic agents such as zidovudine, (Richman *et al.*, 1987) ganciclovir, (Faulds & Heel 1990) and trimethoprim-sulfamethoxazole (Keisu *et al.*, 1990); and myelophthisis caused by cancers such as lymphosarcoma. Other mechanisms for HIV-associated anemia, although uncommon, include vitamin B12deficiency (Remacha *et al.*, 2009) and the autoimmune destruction of red blood cells (Ciaffoni *et al.*, 1992). Direct infection of marrow precursor cells (Cleveland & Liu, 1996) has been hypothesized, but not proven.

People with anemia often suffer decreased quality of life as well as potential increased chance of mortality. Several studies have been performed looking at the quality of life of people with HIV-related anemia. A large study of more than 1,200 people with HIV and cancer showed that low hemoglobin levels are associated with greater fatigue and a poor overall quality of life. The Centers for Disease Control conducted a large study reviewing medical records of HIV-infected patients from January, 1990 through August, 1996 (Sullivan *et al.*, 1998). This study concluded that the incidence of anemia was found to be strongly associated with progression of HIV disease. HIV-infected individuals with anemia were also found to have shorter survival rates. A study was performed at the Johns Hopkins University School of Medicine

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AIDS Clinic to assess the incidence of anemia in their patients. This study looked at a total of 2,348 patients of which 498 had developed anemia. The study showed that untreated anemia is associated with a greater risk of dying, regardless of T-Cell count, opportunistic infection or treatment with antiviral drugs.

METIOLOGIES

The possible etiologies of anemia in patients with HIV infection are; HIV (B19 parvovirus, Mycobacterium avium, complex, Mycobacterium tuberculosis, Histoplasma capsulatum, Coccidioides immitis, Cryptococcus neoformans, Pneumocystis carinii), Medications (Ganciclovir, Zidovudine (AZT), Trimethoprim-sulfamethoxazole, Dapsone, Sulfadiazine Pyrimethamine, Amphotericin B, 5-Flucytosine, Antineoplastics, Interferon-alpha, Cidofovir) and Neoplasms (Non-Hodgkin's lymphoma and Hodgkin's disease).

A study of serum immunoreactive erythropoietin in HIV-infected patients in various stages of illness showed that levels of the hormone failed to rise commensurately with increasing anemia, suggesting that insufficient amounts of erythropoietin may be one cause of anemia in this setting (Sullivan *et al.,* 1998). Other studies have suggested that soluble factors in the serum of HIV-infected patients may inhibit hematopoiesis, or that direct HIV infection of marrow progenitor cells may play a role in producing anemia and other hematologic abnormalities associated with HIV infection (Spivak,1989; Kaslow *et al.,* 1987; Stella *et al.,* 1987).

HEMATOLOGICAL MANIFESTATIONS OF ANAEMIA

Drug-Induced Anemia

Zidovudine (AZT) therapy is probably the most common cause of anemia in HIV-infected patients. In the original phase II clinical trial that demonstrated the efficacy of AZT in patients with advanced HIV disease, statistically significant reductions in hemoglobin levels occurred in 34% of subjects receiving AZT (1,200 mg per day) following 6 weeks of therapy (Folks, *et al.,* 1988). This fall in hemoglobin was accompanied by a progressive rise in erythrocyte mean corpuscular volume that has now become familiar to physicians treating patients with AZT. Thirty-one percent of AZT-treated subjects in the trial required red blood cell transfusions while receiving the drug. Marrow erythroid hypoplasia, aplasia, and megaloblastic maturation have developed as a result of AZT therapy(Richman *et al.,* 1987). Subsequent studies have demonstrated that anemia is less common in patients with relatively less advanced HIV disease and in those receiving reduced dosages of AZT(Walker, 1988; Volberding *et al.,* 1990) for example, clinically significant anemia (hemoglobin < 8 g/dl) occurred in only 1.1% of asymptomatic HIV-infected patients with 200 to 500 CD4+ T lymphocytes/mm^3 treated for a mean of 55 weeks with AZT (500 mg/day)(Walker, 1988). More recent studies of combination antiretroviral therapy have confirmed the relatively low incidence of severe anemia at lower doses of zidovudine (Collier *et al.,* 1990). Despite these findings, many patients receiving the drug in clinical practice will require occasional transfusions or change in drug therapy to ameliorate this toxicity.

Effective therapy for AZT-induced anemia is available in the form of recombinant human erythropoietin. A double-blind, placebo-controlled study demonstrated that recombinant human erythropoietin (100 units/kg 3 times weekly by intravenous bolus) reduced transfusion requirements of AZT-treated HIV-infected patients whose serum levels of endogenous erythropoietin were less than 500 IU per liter (Eron *et al.,* 1995). Significantly fewer erythropoietin-treated patients received transfusions, and those who were transfused received significantly fewer units of red blood cells in comparison to placebo-treated patients. Antimicrobial and antineoplastic agents used for treatment or prophylaxis against HIV-related conditions also cause anemia. For example, dapsone for treatment or prevention of *Pneumocystis carinii* pneumonia (PCP) may cause hemolytic anemia or generalized myelosuppression, (Fischl *et al.,* 1990) and anemia routinely occurs when myelosuppressive chemotherapy is used to treat HIV-related non-Hodgkin's lymphoma.

Anemia Caused by Bone Marrow Infections

Infection with *Mycobacterium avium* complex (MAC) is another common cause of anemia in advanced HIV disease. This infection, diagnosed in up to 18% of patients with advanced HIV disease during the course of their illness, (Medina *et al.,* 1990) causes high-grade bacteremia and widely disseminated infection, usually involving the bone marrow. In such patients, anemia tends to occur out of proportion to other cytopenias (Hawkins, 1986). A study at San Francisco General Hospital examined the relationship between MAC bacteremia and transfusion requirements: patients with positive blood cultures for MAC were 5.23 times more likely to receive red blood cell transfusions than patients with negative blood cultures (Bogner *et al.,* 1990). The benefit of the antimycobacterial therapies currently available for MAC infection is controversial. Although some treatment studies have demonstrated a reduction in symptoms, such as fever, in conjunction with a reduction in the number of organisms in the blood (Jacobson *et al.,* 1990; Shafran *et al.,* 1996) no study of antimycobacterial therapy for MAC infection has shown improvement of the associated anemia.

Infection with B19 parvovirus can also cause anemia in HIV-infected patients (Hoy *et al.,* 1990). B19 parvovirus, the etiologic agent of the childhood exanthem "fifth disease" (erythema infectiosum), has

been recognized for some time as a cause of severe chronic anemia in immunocompromised persons. Parvovirus DNA has been detected in the serum or bone marrow (or both) of some patients with HIV infection and severe anemia. The anemia of parvovirus infection has been successfully treated with infusions of immunoglobulin (400 mg/kg/day over 5 to 10 days) (Mitchell *et al.,* 1990). Other conditions associated with HIV infection can cause anemia as a result of direct involvement of the bone marrow. Tuberculosis, histoplasmosis, cryptococcosis, pneumocystosis, and non-Hodgkin's lymphoma can all infiltrate the bone marrow, (Frickhofen *et al.,* 1990) generally causing pancytopenia.

Other Causes of Anemia

Antierythrocyte antibodies produce a positive direct antiglobulin test in approximately 20% of HIV-infected patients with hypergammaglobulinemia (Northfelt *et al.,* 1991; McGinniss *et al.,* 1986). Although not well characterized, these antibodies behave as polyagglutinins, and it is unclear whether they are directed against specific cell-surface antigens or merely represent nonspecific attachment. Hemolytic anemia in the setting of an HIV-related positive direct antiglobulin test is rare. Gastrointestinal bleeding should also be considered in the evaluation of HIV-infected patients with anemia. In addition to the usual causes of gastrointestinal blood loss, HIV-related infections such as cytomegalovirus colitis and malignancies such as Kaposi's sarcoma and non-Hodgkin's lymphoma may produce clinically significant bleeding. Hypogonadism is relatively common in HIV-infected men, and the associated symptoms and problems (fatigue, weight loss, sexual dysfunction) may also include anemia (Toy *et al.,* 1985). A serum testosterone level should therefore also be included in the evaluation of men with anemia and other symptoms suggestive of possible hypogonadism.

Evaluation of Patients with HIV Infection and Anemia

The following approach is recommended for the evaluation of anemia in patients with HIV infection:

- Conduct a general evaluation for anemia. Look for evidence of blood loss as would be done in any patient with anemia, including an assessment of iron stores (serum iron, iron binding capacity, and ferritin levels), as well as stool tests for occult blood and any other necessary procedures to assess for gastrointestinal bleeding. Test for vitamin B_{12} or folic acid deficiency if the anemia is accompanied by macrocytosis and a suggestive dietary or alcohol history. Clinicians should also consider hemoglobinopathies (sickle cell disease, thalassemia), enzyme deficiencies (glucose-6-phosphate dehydrogenase, pyruvate kinase), and hereditary spherocytosis in patients with appropriate ethnic backgrounds or family histories and suggestive findings on the peripheral blood smear. Obtain a serum testosterone level in men with anemia and other symptoms suggestive of hypogonadism.
- Review the patient's medications. If the patient is receiving AZT and other causes of anemia are excluded, consider a change to another antiretroviral agent. Obtain a serum erythropoietin level to determine whether treatment with exogenous erythropoietin is indicated. If the patient is receiving dapsone or trimethoprim-sulfamethoxazole as prophylaxis for PCP, measure serum bilirubin, lactate dehydrogenase (LDH), methemoglobin, and haptoglobin levels to test for drug-induced hemolysis. If test results suggest hemolysis, obtain direct and indirect antiglobulin tests to detect the rare case of autoimmune hemolysis before ascribing the problem to the drug.
- When anemia occurs in a patient who has other signs and symptoms suggesting infection or neoplasm (fever, fatigue, weight loss, diarrhea), evaluate the patient for these conditions. Obtain mycobacterial blood cultures to assess for disseminated infection with MAC or *M. tuberculosis*. Fungal blood cultures can reveal disseminated infection with *Histoplasma capsulatum*, although such patients are generally gravely ill and have anemia as a relatively minor component of illness. Bone marrow biopsy can aid in the diagnosis of disseminated mycobacterial and fungal infections or lymphoma, although the experience at San Francisco General Hospital and elsewhere suggests that microbiologic or histopathologic examination of other tissues or body fluids usually leads to the diagnosis of these conditions.

B19 parvovirus infection is strongly suggested when bone marrow examination reveals erythroid hypoplasia with giant pronormoblasts. Polymerase chain reaction (PCR)-based assays for parvovirus DNA in serum can also be used to confirm the diagnosis. Consider bone marrow examination to establish this rare diagnosis only after other possibilities have been exhausted.

Thrombocytopenia

Thrombocytopenia is frequently associated with HIV infection. In the Multicenter AIDS Cohort Study, platelet counts were measured in over 1,500 HIV-seropositive participants who did not have CDC-defined AIDS; 6.7% of participants had platelet counts of less than 150,000 cells/mm^3 on at least one semiannual visit, and 2.6% of participants had platelet counts of less than 150,000 cells/mm^3 on two successive semiannual visits. In a Swiss study, platelet counts of less than 100,000 cells/mm^3 were noted in 9% of 321 HIV-seropositive injection drug users and in 3% of 359 HIV-seropositive homosexual men (Laudat *et al.,* 1995). A smaller study from London reported platelet counts of less than 150,000 cells/mm^3 in 30% (6

of 20) of patients with advanced HIV disease and 8% (5 of 59) of patients with persistent generalized lymphadenopathy (Jost *et al.,* 1988). Possible etiologies of thrombocytopenia in patients with HIV infection include immune-mediated destruction, thrombotic thrombocytopenic purpura, impaired hematopoiesis, and toxic effects of medications. In many instances, however, thrombocytopenia is a relatively isolated hematologic abnormality associated with a normal or increased number of megakaryocytes in the bone marrow and elevated levels of platelet-associated immunoglobulin. These patients have the clinical syndrome commonly referred to as immune thrombocytopenic purpura (ITP).

HIV-Related Immune Thrombocytopenic Purpura

A patient with thrombocytopenia has true HIV-ITP if there is no other condition or treatment that could cause thrombocytopenia. Most such patients are otherwise well. In fact, HIV-ITP is most often an early manifestation of HIV infection, occurring before the development of any CDC AIDS-defining condition. CD4+ lymphocyte counts in reported series of patients with HIV-ITP have averaged between 300 and 600 cells/mm^3. HIV-ITP is therefore commonly included among those conditions characterizing the middle-stage HIV disease (Murphy *et al.,* 1987). ITP typically improves as HIV disease progresses.

In 1982, Morris et al. described a cluster of 11 cases of ITP in homosexual men in New York City (Abrams, 1988). The demographic characteristics and immunologic profiles of their patients were similar to those being described in patients with advanced HIV disease. Subsequently, ITP was reported in HIV-infected injection drug users, hemophiliacs, transfusion recipients, and children (Morris *et al.,* 1982). Several hypotheses have been advanced to explain the pathogenesis of HIV-ITP. One theory holds that circulating immune complexes are nonspecifically deposited on platelet membranes, resulting in reticuloendothelial clearance (Ratner, 1989; Walsh *et al.,* 1984). Studies have shown that these immune complexes contain anti-HIV gp120 and complementary anti-idiotypic antibody (Karpatkin et *al.,* 1988). After noting the improvement in platelet counts of HIV-ITP patients treated with AZT, investigators also sought to define a more central role for HIV itself in the pathogenesis of HIV-ITP (Karpatkin & Nardi,1989). They performed ultrastructural analysis of bone marrow megakaryocytes from patients with HIV-ITP and found unique structural aberrations. In addition, HIV RNA was shown by in situ hybridization to be expressed within the cells. The authors suggested that direct infection of megakaryocytes by HIV may impair platelet production and contribute to thrombocytopenia. Regardless of the actual mechanism responsible for platelet destruction, thrombocytopenia in HIV-infected patients may be compounded by impaired ability to produce platelets in sufficient numbers (Zucker-Franklin & Cao,1989).

Diagnosis

The classic approach to the diagnosis of ITP in non-HIV-infected patients is to consider it a "diagnosis of exclusion," meaning that any other cause of low platelet production or peripheral platelet destruction must be excluded before the diagnosis of ITP may be applied to a patient with a low platelet count. The same general approach should be taken in cases of possible HIV-ITP.

Therapy

Treatment of HIV-ITP should be reserved for patients with clinically significant symptoms such as recurrent epistaxis, gingival or subconjunctival bleeding, or gastrointestinal hemorrhage. Therapy is also recommended for hemophiliacs with HIV-ITP because of the substantial morbidity and mortality associated with bleeding in this group (Ballem *et al.*,1992) Only in these situations does it seem worthwhile to subject HIV-infected patients to the troublesome toxicity and questionable efficacy of most standard therapies for ITP. In contrast, AZT and interferon-alpha therapy can raise the platelet count while simultaneously providing antiretroviral activity. Therefore, these agents are attractive options in the treatment of HIV-ITP. Currently employed combination antiretroviral therapy should be capable of ameliorating HIV-ITP through its ability to markedly reduce plasma HIV viremia. Specific observations in support of this hypothesis have not been reported, presumably due to the rarity of HIV-ITP among cohorts of patients treated with the new combination therapies.

For treatment of ITP in patients without HIV infection, therapy with corticosteroids, cytotoxic agents, the attenuated androgen danazol, intravenous immunoglobulin infusions, plasmapheresis, interferon-alpha, and splenectomy have all been used with varying degrees of success. Many of these methods have also been used for treatment of HIV-ITP, but relatively unsatisfactorily. Walsh et al. treated 17 HIV-ITP patients using standard prednisone therapy for ITP. (Ragni *et al.,* 1990) Platelet counts increased from a mean of 21,000 to more than 100,000 cells/mm^3 in 8 patients, and to more than 50,000 cells/mm^3 in 8 others, but 13 patients relapsed when the prednisone was tapered. Other investigators reported similar unsatisfactory outcomes with corticosteroid therapy. (Walsh *et al.*,1985; Oksenhendler *et al.*,1987) There are no data to support or refute the importance of immunosuppressive effects of corticosteroid therapy in patients with HIV infection, but it seems prudent to avoid such effects when possible.

Various authors have reported responses to splenectomy in HIV-ITP of 60 to 100% of cases, (Abrams *et al.*,1986; Schneider *et al.*,1987; Ravikumar

et al.,1989) with low rates of surgical morbidity. Concerns have been raised regarding the possible immunosuppressive effect of splenectomy in patients with HIV infection (Ferguson,1988) In addition, some surgeons hold that HIV infection impairs wound healing, so they are therefore reluctant to recommend operation. Low-dose splenic irradiation can also raise the platelet count in some patients with HIV-ITP, presumably by acting as a "non-surgical splenectomy" (Barbui *et al.*, 1987). The relatively unimpressive results, as well as the extremely high cost of intravenous immunoglobulin therapy, have limited its use. A new product, anti-Rho (D) immune globulin (trade name WinRho), was licensed recently for use in the treatment of ITP and HIV-ITP. Investigators studying this product reported improved efficacy in comparison to historical experience with other immunoglobulin preparations. It appears that treatment with anti-Rho (D) immune globulin can produce more sustained increases in platelet count in selected patients with HIV-ITP with reduced toxicity and frequency of administration (Needleman *et al.*, 1992).

In a number of the early studies of AZT therapy for HIV infection, platelet counts were noted to rise during treatment. In a subsequent prospective, placebo-controlled, blinded study of AZT therapy for HIV-ITP,(Bussel *et al.* ,1991) platelet counts increased from 1.1- to 3.8-fold in all patients over the course of 8 weeks of AZT treatment; no change in platelet count was noted during placebo treatment. AZT therapy in this study consisted of 2 g per day for 2 weeks, followed by 1 g per day for 6 weeks; one patient could tolerate only 250 mg per day because of leukopenia but still had a twofold rise in platelet count. Based on current understanding of the pathogenesis of HIV-ITP, potent combination antiretroviral therapy should produce similar or better results than are seen with AZT monotherapy, but objective evidence on this point is lacking. Several case reports and small case series have described the use of small doses of interferon-alpha in the treatment of HIV-ITP. Modest improvement in platelet counts have been obtained and the treatment has caused relatively little toxicity. For example, in a series of 13 patients evaluated during 16 weeks of therapy with interferon-alpha 2b (3 million units subcutaneous three times weekly), 9 patients obtained clinically meaningful improvement of their thrombocytopenia.(Swiss Group for Clinical Studies on the Acquired Immunodeficiency Syndrome,1988) Subjective and hematologic toxicities were mild and tolerable, and minor bleeding problems improved in all patients so affected.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a clinical syndrome characterized by the classic pentad of fever, neurologic dysfunction, renal dysfunction, microangiopathic hemolyticanemia, and thrombocytopenia. The finding of hyaline microvascular thrombi in tissue biopsy specimens supports the diagnosis. Abnormal interaction between platelets and endothelium are thought to be responsible for the clinical and pathologic findings, but the mechanism accounting for this observation remains undefined. Plasmapheresis is generally accepted as standard therapy for TTP, although plasma infusions, exchange transfusions, antiplatelet drug therapy, corticosteroids, and splenectomy have all been used with varying degrees of success (Northfelt *et al.*, 1995).

A number of cases of TTP occurring in patients with HIV infection have been described in the medical literature. Data from one center have been interpreted to show a statistically significant association of TTP with HIV infection (Shepard & Bukowski,1987). In most of the reported cases, there was no diagnosis of CDC-defined AIDS prior to the development of TTP, although several patients had symptomatic HIV disease (persistent lymphadenopathy, oral candidiasis) at presentation. This observation, along with relatively high CD4 lymphocyte counts or CD4/CD8 lymphocyte ratios reported in some of the cases, suggests that TTP, like HIV-ITP, is an early manifestation of HIV infection. The etiology of TTP in patients with HIV infection has not been established. Most patients with HIV-related TTP have been successfully treated with plasmapheresis in conjunction with antiplatelet agents, corticosteroids, or both. Because HIV-infected patients with TTP appear to have relatively well-preserved immune function and a good response to plasmapheresis can be expected, prompt diagnosis and appropriate therapy are essential.

Other Causes of Thrombocytopenia in HIV Disease

Any of the infectious or neoplastic conditions that involve the bone marrow and any of the medications that cause generalized myelosuppression in patients with HIV infection can produce thrombocytopenia. HIV-infected patients are also susceptible to developing thrombocytopenia for reasons unrelated to their HIV infection, such as alcohol use, splenomegaly and liver disease, or drug effects (heparin, quinidine); clinicians must always consider these possibilities when evaluating the thrombocytopenic HIV-infected patient.

Evaluation of Patients with HIV Infection and Thrombocytopenia

The following approach is recommended for the evaluation of thrombocytopenia in patients with HIV infection:

As in HIV-infected patients with anemia, patients with thrombocytopenia should undergo a general evaluation in search of the common causes of this abnormality. A bone marrow biopsy should be examined to identify cytotoxic or alcohol or drug-

related effects. The marrow should be examined for the presence of lymphoma or opportunistic infections such as fungi or mycobacteria that would result in reduced megakaryocyte numbers and hence reduced platelet production. Other causes of peripheral platelet destruction must also be sought, including splenic sequestration resulting from liver disease with portal hypertension, drug-induced ITP, lymphoma-associated ITP, TTP, or disseminated intravascular coagulation.

The finding of platelet-associated immunoglobulin or immune complexes strengthens the diagnosis of HIV-ITP but is neither sufficient nor necessary for the diagnosis. Most hematologists consider examination of the bone marrow useful but not essential in a patient with suspected ITP; the finding of a normal or increased number of megakaryocytes in the marrow is consistent with the diagnosis. In clinical practice, patients with known HIV infection, relatively well-preserved immune function as documented by high CD4+ t-lymphocyte count and no history of opportunistic infections, and thrombocytopenia as an isolated hematologic abnormality are sometimes given the diagnosis of HIV-ITP without being subjected to more extensive laboratory testing. Because most patients with HIV-ITP require no specific therapy, this limited diagnostic approach is appropriate.

Granulocytopenia and Abnormal Granulocyte Function

Granulocytopenia is a problem commonly encountered in patients with HIV infection. Although low granulocyte counts usually reflect the toxicity of therapies for HIV infection or associated conditions, studies of untreated patients have also shown a high incidence of granulocytopenia, particularly in patients with more profound immunodeficiency. For example, the Multicenter AIDS Cohort Study found that 0.8% of HIV-seropositive patients with mean CD4+ T lymphocyte counts of greater than 700 cells/mm3 had abnormally low granulocyte counts, whereas granulocytopenia was present in 13.4% of those with mean CD4+ T lymphocyte counts below 249 cells/mm3(Maciejewski *et al.,* 1994). Zon and Groopman noted low granulocyte counts in 13% of asymptomatic HIV-seropositive patients and in 44% of those with frank CDC-defined AIDS (Groopman,1990).

The pathogenesis of granulocytopenia in patients with HIV infection is multifactorial An autoimmune mechanism involving antigranulocyte antibodies (Hawkins, 1986) and impaired granulopoiesis (Horsburgh, 1991) has been postulated, but not yet proved, to account for granulocytopenia in some patients. Any infiltrative process involving the bone marrow (infection, malignancy) may also produce granulocytopenia. In clinical practice, however, drug toxicity is responsible for most of the granulocytopenia seen in patients with HIV infection. It is important to note that in a one study, investigators showed a good correlation between the level of the absolute granulocyte count and the risk of hospitalization for a significant bacterial infection in weeks immediately following the absolute neutrophil count (ANC) (Abrams *et al.,* 1986).

Drug-Induced Granulocytopenia

AZT therapy is probably the most common cause of low granulocyte counts in patients with HIV infection. Severe granulocytopenia (< 500 cells/mm3) developed in 16% of AZT-treated patients in the original placebo-controlled study of AZT therapy for advanced HIV disease and symptomatic middle-stage HIV disease; only 2% of placebo-treated patients became granulocytopenic to this degree.(6) Despite the relatively high frequency of AZT-induced granulocytopenia, there were no reported episodes of bacterial infection or sepsis in the study group. In subsequent studies of AZT therapy,(8,9,50) the observed risk of bacterial infection was low, reflecting the brief duration of AZT-induced granulocytopenia; the dosage of AZT was reduced or discontinued when the granulocyte count fell below the range of 500 to 1,000 cells/mm3. As stated previously, low ANC is associated with increased risk of hospitalization for significant bacterial infection in weeks following the ANC. Granulocyte recovery is generally prompt following discontinuation of AZT therapy.

Shaunak and Bartlett described their experience in treating 30 patients with severe, recurrent (three or more episodes) AZT-induced granulocytopenia (Ravikumar *et al.,* 1989). The total follow-up time was 493 months (41.1 patient-years) and the granulocyte count was less than 1,000 cells/mm3 for 41% of that time. AZT therapy was reduced or discontinued when the granulocyte count fell below the range of 500 to 1,000 cells/mm3. Patients with granulocyte counts of less than 500 cells/mm3 had an incidence of bacterial infection that was 230% higher than in patients with granulocyte counts of 500 to 1,000 cells/mm3 (seven infections in 40 months vs. nine infections in 169 months). The authors concluded that AZT therapy can be continued despite granulocytopenia without a major increase in the incidence of bacterial infection provided that the granulocyte count is not lower than 500 cells/mm3.

Ganciclovir therapy for symptomatic cytomegalovirus infection is another common cause of granulocytopenia in patients with advanced HIV disease. Jacobson et al. observed absolute granulocyte counts of less than 800 cells/mm3 in 10 of 32 patients receiving chronic daily maintenance ganciclovir therapy (Ferguson, 1988). Four patients developed central venous catheter-associated bacteremia; all had granulocyte counts of greater than 1,200 cells/mm3 when bacteremia occurred. In other studies reviewed by Jacobson, bacterial infection was a very rare

complication of ganciclovir-induced granulocytopenia, (Barbui, *et al.*, 1987) possibly reflecting the brief duration of ganciclovir-induced granulocytopenia attributable to the discontinuation of ganciclovir therapy when the granulocyte count falls below 500 to 1,000 cells/mm3. Recovery is generally prompt.

A number of other medications commonly used in the setting of HIV infection can cause granulocytopenia. Trimethoprim-sulfamethoxazole and pentamidine are standard therapy for PCP. Granulocytopenia has been reported in a high percentage of patients receiving these antibiotics in clinical trials, but bacterial infections have not occurred as a consequence (Needleman *et al.*, 1992; Bussel *et al.*, 1991). Interferon-alpha therapy, both alone (Northfelt *et al.*, 1995; Shepard & Bukowski, 1987) and in combination with AZT,(Leaf *et al.*, 1988) can also cause granulocytopenia.

Antineoplastic chemotherapy is probably the most common cause of low granulocyte counts in patients without HIV infection. Granulocytopenia secondary to cancer chemotherapy also complicates treatment of HIV-infected patients, perhaps to an even greater extent as a result of impaired bone marrow function. There are few reports, however, describing the types or incidence of granulocytopenia-related infections in this setting. With a relatively aggressive combination chemotherapy regimen (doxorubicin (Adriamycin) plus bleomycin plus vincristine ("ABV")) in the treatment of advanced HIV-related Kaposi's sarcoma, granulocytopenia (less than 1,000 cells/mm3) occurred in 11 of 33 patients, and bacterial infections developed in 5 (Van der Lelie *et al.*, 1987). Patients with HIV-related non-Hodgkin's lymphoma frequently require hospitalization for empiric antibiotic therapy when granulocytopenia (< 500 cells/mm3) and fever develop following chemotherapy (Jacobson *et al.*, 1997). In a review of 99 such hospitalizations, 23 episodes of bacteremia were identified (Pinching *et al.*, 1989). In summary, drug-induced granulocytopenia is common in patients with HIV infection. When the granulocyte count falls below 500 cells/mm3, the risk of infection and sepsis is significant, an observation in accord with similar findings in other disease states. Therefore, empiric antibiotic therapy need not be prescribed in cases of mild granulocytopenia resulting from drug therapy or underlying disease states. Rather, antibiotics are reserved for those situations in which frank evidence of bacterial infection is present, or the granulocyte count is below 500 cells/mm3 and is expected to remain at that level for a prolonged period of time, as in the aftermath of chemotherapy for HIV-associated malignancies (Shaunak Bartlett, 1989).

Defective Granulocyte Function

Qualitative functions of granulocytes from patients with HIV infection have been studied in vitro, and a number of abnormalities have been noted. Defective chemotaxis, deficient degranulation responses, and ineffective phagocytosis and killing have all been reported (Jacobson *et al.*, 1988; Jacobson, 1990; Gordin *et al.*, 1984). The clinical importance of these observations has not been clearly established.

Evaluation of Patients with HIV Infection and Granulocytopenia

The following approach is recommended for the evaluation of granulocytopenia in patients with HIV infection:

Carefully review the patient's medications. Most cases of granulocytopenia are due to drug toxicity. Discontinue myelosuppressive agents if the patient's granulocyte count falls below 500 cells/mm3. Alternative therapies are available in many situations to substitute for the offending agent; in some cases, dosage alterations may suffice. Colony-stimulating factors (CSFs) are also being used more widely in clinical practice to raise granulocyte counts in patients who must remain on toxic therapies. Perform bone marrow examination in patients with granulocytopenia of uncertain etiology. The marrow should be examined for lymphoma or opportunistic infections such as fungi or mycobacteria, which would result in reduced granulocyte production.

Uses of Myeloid Colony-Stimulating Factors in HIV Disease

As just explained, anemia and granulocytopenia frequently result from the use of medications prescribed for treatment of HIV infection and related conditions. Such treatment is often limited primarily by the development of these cytopenias. The use of erythropoietin to ameliorate the anemia occurring with AZT therapy was described previously and provides an example of the use of a hematopoietic growth factor to alleviate bone marrow toxicity and permit continued use of a critical therapy for the HIV-infected patient. Similarly, efforts have been made to alleviate the granulocytopenia in HIV-infected patients with the use of myeloid growth factors.

Application and Efficacy

The first human trial of a myeloid growth factor was conducted in patients with advanced HIV disease and granulocytopenia (Wharton *et al.*, 1986). A rapid, dose-related increase in granulocytes, monocytes, and eosinophils occurred, accompanied by increases in total marrow cellularity. Toxicities included fevers, facial flushing, skin rash, and phlebitis at infusion sites. Long-term subcutaneous administration of GM-CSF in HIV-infected patients resulted in similar, but sustained, effects (Sattler, *et al.*, 1988).

Early studies of therapy for HIV-related non-Hodgkin's lymphoma demonstrated that standard chemotherapy for lymphoma is poorly tolerated by patients with HIV infection due to severe myelosuppression. Therefore, two clinical trials have

assessed the ability of GM-CSF to decrease the myelosuppressive effects of such chemotherapy. In one study, successive cohorts of patients with HIV-related non-Hodgkin's lymphoma received GM-CSF along with escalating doses of the m-BACOD (methotrexate, bleomycin, Adriamycin, cyclophosphamide, Oncovin, dexamethasone) regimen (Rios *et al.,* 1985). Myelotoxicity was acceptable in all groups, including the final (standard-dose m-BACOD) group, whose mean granulocyte nadir was 1,227 cells/mm^3. In the second study, patients with HIV-related non-Hodgkin's lymphoma were treated with a minor modification of the standard CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone) chemotherapy regimen (Real *et al.,* 1986). Approximately 50% of the patients were randomized to receive additional therapy with GM-CSF. The group treated with GM-CSF had higher mean granulocyte nadirs, shorter mean duration of granulocytopenia, fewer chemotherapy cycles complicated by granulocytopenia and fever, fewer days of hospitalization, and fewer dose reductions or delays in chemotherapy administration. These studies demonstrate that chemotherapy for HIV-related non-Hodgkin's lymphoma can be given with less toxicity when accompanied by therapy with GM-CSF to reduce myelosuppression. Additional clinical trials have assessed the efficacy of GM-CSF in reducing the myelosuppressive effects of other treatments commonly used in patients with HIV infection (Kovacs *et al.,* 1989). GM-CSF therapy has alleviated granulocytopenia induced by AZT, ganciclovir, and interferon with AZT. The toxicities of GM-CSF (fever, rash, bone pain, myalgia) were similar in all these studies.

The effect of GM-CSF therapy on HIV expression has not been fully clarified. Several studies have shown no consistent change in HIV p24 antigen serum levels or ability to recover virus from peripheral blood mononuclear cells of patients treated with GM-CSF (Gill *et al.,* 1990; Kaplan *et al.,* 1991). Kaplan and colleagues reported, however, that the median serum HIV p24 antigen level rose to 234% of baseline 1 week after administration of GM-CSF in patients being treated for HIV-related non-Hodgkin's lymphoma, whereas the median level in control patients fell to 18% of baseline (Jacobson *et al.,* 1997). Similarly, Pluda and co-workers found that serum levels of HIV p24 antigen rose significantly in patients treated with GM-CSF (Northfelt *et al.,* 1990). Both groups therefore cautioned that GM-CSF may stimulate HIV replication, as reflected by increases in antigen production.

Granulocyte CSF (G-CSF) has also been used in an attempt to overcome the myelosuppression induced by AZT. This growth factor has been shown to have no stimulatory effect on HIV replication in macrophages *in vitro* (Hughes, *et al.,* 1997). In one clinical trial, erythropoietin and G-CSF were given simultaneously to 20 patients who were divided into cohorts receiving various doses of AZT (Ellis *et al.,* 1988). Six patients were removed from the study after developing transfusion-requiring anemia, but all were maintained with acceptable granulocyte counts (> 1,500 cells/mm^3). Toxicities were insignificant, and no significant changes in HIV replication were noted. Additional studies have documented the benefit of G-CSF therapy in HIV-infected patients (Valone *et al.,* 1984). In summary, CSFs are likely to play a significant role in the treatment of patients with HIV infection. They have proven useful both in reversing cytopenias due to HIV infection itself and in ameliorating the toxicity of AZT and other therapies given for HIV-related conditions. Concerns regarding the stimulatory effect of GM-CSF on HIV replication must be addressed before this agent can be more widely used.

Prescribing Myeloid Growth Factors for Patients with HIV Disease

Marketing of the myeloid growth factors occurred before clinical trials could be completed to fully define the indications for their use. Therefore, formal guidelines regarding the use of these agents do not yet exist. Nevertheless, many clinicians are incorporating the use of CSFs into the treatment of patients with HIV disease who require myelosuppressive therapies. G-CSF is being used to ameliorate granulocytopenia resulting from ganciclovir therapy for cytomegalovirus disease, antibiotic therapies for PCP and toxoplasmic encephalitis, and antiretroviral therapy for HIV infection. G-CSF is also being used widely in patients requiring myelosuppressive chemotherapy for Kaposi's sarcoma and HIV-related non-Hodgkin's lymphoma. GM-CSF has not been used widely because it causes more severe side effects than G-CSF, and there is concern that it may cause an undesirable increase in HIV replication.

It seems reasonable to prescribe G-CSF for patients who would otherwise be forced to discontinue important therapies because of critical granulocytopenia (< 500 cells/mm^3). Initially, the drug should be administered at a dose of 300 mg per day. The granulocyte count should be monitored closely, and the dose of G-CSF adjusted to the smallest amount necessary to maintain the granulocyte count in an acceptable range. Minimal effective doses should be used because of the substantial cost of this therapy. Physicians should be aware that health insurers may refuse to reimburse for G-CSF used for indications other than those approved by the U.S. Food and Drug Administration because of the high cost. G-CSF is currently licensed for treatment of granulocytopenia in patients receiving cancer chemotherapy.

Hemostatic Abnormalities

A number of studies have evaluated prolonged activated partial thromboplastin times (aPTT), which occasionally are detected in patients with HIV infection. Antiphospholipid antibodies have been detected in such patients; these IgG or IgM antibodies are directed against phospholipid moieties and therefore interfere *in vitro* with the action of the thromboplastin used in the aPTT test. Antiphospholipid antibodies, including lupus anticoagulants and anticardiolipin antibodies, have been detected in a variety of disorders. They are rarely associated with clinical bleeding but, paradoxically, have been implicated in thrombotic disease (Murphy *et al.*, 1988).

Although lupus anticoagulants and anticardiolipin antibodies have been detected with high frequency in selected cohorts of HIV-infected patients, (Groopman *et al.*, 1987) no associated thrombotic or hemorrhagic tendencies have been noted. One group of investigators (Smith *et al.*, 1990) has noted that thrombotic skin lesions may occur in HIV-infected patients with antiphospholipid antibodies that appear similar to lesions of Kaposi's sarcoma on gross inspection but have characteristic histopathologic features.

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