Hematologic Complications of HIV Infection

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Hematologic complications of HIV disease are commonly encountered by physicians and other health-care workers caring for patients infected with this virus. Ineffective hematopoiesis, infiltrative diseases of the bone

Introduction

Hematologic complications of HIV infection are common and challenge physicians treating patients at all stages of HIV disease [1,2]. Ineffective hematopoiesis from direct suppression by HIV infection or excessive cytokine secretion [3-5], infiltrative bone marrow disease of infectious or neoplastic origin, nutritional deficiencies, and drug effects all impact on hematopoiesis.

Peripheral Cytopenias

The presence of isolated or trilineage cytopenias is frequently noted in patients infected with HIV. Anemia, granulocytopenia, and thrombocytopenia occur in 17%, 8%, and 13%, respectively, of asymptomatic HIV-infected individuals [6], and these percentages increase with advancing HIV disease.

Anemia

Anemia is the most common hematologic abnormality noted in patients with HIV infection [7] (see Table 1). It may develop in patients with persistent lymphadenopathy who are otherwise asymptomatic but is more prevalent in patients with overt AIDS, occurring in 66% to 85% of those with advanced disease [5,6].

The anemia appears to be due to ineffective erythropoiesis, possibly as a direct consequence of HIV infection of erythroid precursors or, more likely, as a result of the inappropriate release of tumor necrosis factor (TNF), an inhibitor of erythroid maturation in vitro [7-9]. The anemia is typically classified as an anemia of chronic disease, characterized by a low reticulocyte count, elevated ferritin level, but adequate iron stores noted on bone marrow biopsy. Review of the peripheral blood smear generally reveals normocytic, normochromic red blood cells (RBCs).

Common Causes--Infiltrative disease of the bone marrow caused by Mycobacterium avium complex commonly causes isolated anemia in patients with advanced HIV disease [10]. The most profound anemias, with hematocrit concentrations in the 15% to 20% range, occur in patients with mycobacterial disease. Other infiltrative processes of the bone marrow, such as fungal infections and lymphoma, may also cause profound anemia but are usually associated with decrements in the other cell lines. Anemia associated with constitutional symptoms, such as fever, night sweats, and weight loss, should be evaluated with a bone marrow biopsy to rule out an infiltrative bone marrow condition.

Persistent infection with B19 parvovirus has been associated with intractable anemia in immunosuppressed patients [11,12]. Classically associated with transient aplastic crises in patients with underlying hemolytic diseases or erythroblastosis fetalis, parvovirus selectively infects actively replicating erythroid precursors, resulting in RBC lysis and erythroid hypoplasia. Clearance of this infection is mediated by an intact humoral response; thus, immunocompromised patients may fail to clear the infection [13,14] or maintain an adequate IgG antibody response [15].

Diagnosis of B19 parvovirus infection is made by serologic studies or bone marrow examination. The presence of giant, abnormal pronormoblasts is typical of parvovirus infection, (Figure 1) and in situ hybridization, using sequence-specific DNA probes for B19 parvovirus, confirms the diagnosis.

Therapy for this disorder includes a course of intravenous or intramuscular immunoglobulin, packed RBC transfusions (if indicated), and folate therapy.

Less common causes of anemia include antibody-mediated hemolysis and nutritional deficiencies. The presence of RBC autoantibodies is common in patients at all stages of HIV infection. However, these autoantibodies rarely are associated with clinically significant hemolysis [16,17].
Nutritional deficiencies described in patients with HIV infection include disorders of iron metabolism or iron deficiency and occult vitamin B12 deficiency. Folate deficiency does not appear to be more prevalent in this patient population. Iron deficiency with a microcytic, hypochromic anemia may result from chronic blood loss secondary to Kaposi’s sarcoma or lymphomatous involvement of the gastrointestinal tract. Thrombocytopenia may lead to chronic blood loss, resulting in iron deficiency. Vitamin B12 deficiency secondary to gastrointestinal malabsorption has been described increasingly in patients with AIDS. Low serum vitamin B12 levels associated with altered cobalamin transport proteins or abnormal absorption of vitamin B12 secondary to chronic diarrhea have been observed [5,18-20]. Occult vitamin B12 deficiency may worsen the anemia associated with zidovudine (Retrovir) [21]. Therefore, it is prudent to monitor vitamin B12 levels periodically in patients with chronic gastrointestinal dysfunction, especially those receiving zidovudine therapy.

**Leukopenia**

Infection with HIV affects the lymphocyte, neutrophil, and macrophage-monocyte cell lines. Despite the hypergammaglobulinemia noted in patients with HIV disease, they exhibit both defective cellular immunity and dysregulated humoral immunity. The hallmark of HIV infection is the progressive depletion of CD4+ lymphocytes [22]. This decrement presumably occurs through direct viral invasion of these cells. Early in HIV infection, one may see an initial increase in the CD8+ population before a decline in the number of CD4+ cells is noted. Infection of macrophages and monocytes and the triggering of an autoimmune response are two other mechanisms by which lymphocyte depletion may occur [8]. Normally, activated T-lymphocytes and monocytes produce cytokines or growth factors necessary for stem cell growth and differentiation. Decreased production of these cytokines may result from HIV invasion of these cells. As with anemia, neutropenia is a frequent complication of HIV infection, but it is generally caused by the use of antiretroviral drugs or drugs used to treat opportunistic infections (see “Hematologic Consequences of HIV Therapy” below). Neutropenia is noted in 8% of asymptomatic individuals [6] and increases in frequency with advancing disease and therapeutic interventions.

The most common cause of neutropenia not due to drug therapy appears to be ineffective granulopoiesis [23]. Antineutrophil antibodies have been implicated in certain circumstances [4,5,24,25], but their prevalence and clinical significance are not well understood. Defects in qualitative functions, such as defective polymorphonuclear leukocyte chemotaxis, deficient degranulating responses, inhibition of leukocyte migration, and ineffective killing have all been reported [26,27], but their clinical importance remains elusive. Similarly, HIV-infected monocytes exhibit marked reductions in chemotaxis and phagocytosis in in vitro studies [22].

**Thrombocytopenia**

The most common platelet abnormality found in HIV-infected patients is thrombocytopenia, perhaps due to platelet-associated immunoglobulin [28]. Other causes of HIV-related thrombocytopenia include circulating immune complexes that precipitate on the platelet surface [28], cross-reactive antibodies to platelet surface glycoproteins [29], and direct retroviral infection of megakaryocytes [30-32]. Most patients with HIV-related immune thrombocytopenia have only minor submucosal bleeding, characterized by petechiae, ecchymoses, and occasional epistaxis. Rare patients have gastrointestinal blood loss. Unlike non-HIV-related immune thrombocytopenia, mild splenomegaly may occur, especially in patients with generalized lymphadenopathy. Laboratory findings reveal isolated thrombocytopenia, generally without concomitant anemia or leukopenia. Examination of the peripheral blood smear and bone marrow biopsy are nonspecific, except for decreased circulating platelet forms and increased numbers of megakaryocytes seen in the bone marrow.

Drug-induced thrombocytopenia should be ruled out in these patients, as in non-HIV-infected patients presenting with isolated thrombocytopenia. Medications that have thrombocytopenia as a side effect should be discontinued.

**Immediate Restoration of Platelet Count**—For autoimmune-mediated thrombocytopenia, steroid and immunoglobulin therapy can be initiated for patients needing immediate restoration of the platelet count. This may include patients who are experiencing bleeding, those who will be undergoing a splenectomy procedure, or those in whom the platelet count is dangerously low and the treating physician wishes to raise the count immediately. The response of patients with HIV-related immune thrombocytopenia to steroid therapy is variable, and the risk of further immune suppression is real. Often, the platelet count falls as the steroid dose is tapered. Splenectomy has been a successful therapeutic intervention for patients who fail to respond to steroid therapy and generally is not associated with greater morbidity or mortality than in patients with non-HIV-associated immune thrombocytopenia [33,34].
As mentioned, intravenous gammaglobulin (400 mg/kg/d for 4 to 5 days) may be used to raise the platelet count rapidly, although its effects are transient, lasting 2 to 3 weeks [35]. The probable mechanism of its effect is blockade of the reticuloendothelial system. The high cost and transient nature of immunoglobulin therapy limit its use to situations in which acute bleeding is occurring or as a preoperative intervention for patients undergoing splenectomy when rapid elevation of the platelet count is necessary.

Although platelet transfusions generally are not indicated in patients with thrombocytopenia of immune origin, treatment with intravenous gammaglobulin before transfusion in emergency situations may improve platelet elevation.

**Nonimmediate Restoration of Platelet Count**—For patients who do not require an immediate increase in platelet count, the institution of antiretroviral therapy, if the patient is not yet on such therapy, may be warranted. Normalization and partial responses of platelet counts have been noted with the institution of zidovudine therapy [36,37]. Interferon-alfa (Intron A, Roferon-A) also has been shown to be efficacious in treating patients with HIV-associated immune thrombocytopenia in several small studies, although it may be more beneficial in patients with less advanced HIV disease [38-40]. Partial responses appear to be more common than complete normalization of platelet counts, and the drug is relatively well-tolerated at doses of 3 million units given subcutaneously three times a week. Intravenous or intramuscular administration of anti-D immunoglobulin has been shown to benefit some Rh-positive patients who, preferably, have not had a splenectomy [41-43]. The presumed mechanism is Fc-receptor blockade by antibody-coated RBCs substituting for the antibody-coated platelets. Clinically significant hemolysis does not appear to complicate this approach [43]. The nonandrogenizing testosterone danazol (Danocrine), initially thought to effectively reverse HIV-related thrombocytopenia, has not proved to be efficacious in large-scale clinical trials. Less widely accepted interventions include vincristine and plasmapheresis.

**Observation**—In the spectrum of HIV-infected individuals, patients with isolated thrombocytopenia associated with HIV infection are generally the most healthy. Clinical bleeding is minimal in these patients, responses to therapeutic interventions are variable, and spontaneous remissions do occur. Thus, a viable alternative is to simply observe the patient closely and institute no therapies directed at correcting the thrombocytopenia until necessary.

**Hematologic Consequences of HIV Therapy**

Many therapeutic interventions contribute to HIV-related hematologic disorders (Table 2).

**Antiretroviral Agents**

Zidovudine, one of the most widely used drugs in these patients, affects all three hematopoietic cell lines, and in vitro studies have demonstrated its toxicity to myeloid and erythroid precursors [44]. As a thymidine analog, zidovudine's primary action is termination of reverse-transcriptase activity of the HIV virus. Zidovudine may also inhibit DNA polymerases, thus impairing normal hematopoiesis in the host [5,21].

Other nucleotide analogs used for antiretroviral therapy, such as ddC (zalcitabine [Hivid], ddl (didanosine [Videx]), d4T (stavudine [Zerit]), and 3TC (lamivudine), and the protease inhibitors are associated with less bone marrow toxicity. In a large-scale collaborative study of patients receiving zidovudine therapy [21], significant anemia developed in 34% of patients, 21% of whom required blood transfusions; neutropenia developed in 16%; and thrombocytopenia developed in 12%. Advanced HIV disease, preexisting cytopenias, and low vitamin B12 levels were associated with a greater risk of zidovudine-induced hematologic toxicities. Administration of zidovudine results in an increase in the mean corpuscular volume of RBCs in most patients; however, bone marrow examination usually reveals hypoplasia, aplasia, or maturation arrest [5,21,45,46]. Overt megaloblastic changes are not always noted. The myelosuppression seen with zidovudine therapy is not permanent and can be reversed by using lower doses or discontinuing the drug [5,21].

**Antimicrobial and Chemotherapeutic Agents**

Cytopenias may also complicate therapy of HIV-associated opportunistic infections (Table 2). The use of antimicrobial agents (eg, sulfa derivatives) and antiviral drugs (eg, ganciclovir [Cytovene]) may cause isolated or trilineage cytopenia. Dapsone (Dapsone) therapy may induce methemoglobinemia or hemolysis in patients who are deficient in glucose 6-phosphate-dehydrogenase (G-6-PD). Drug-induced neutropenia may result from medications used to treat such infections as *Pneumocystis carinii* pneumonia, toxoplasmosis, and cytomegaloviral retinitis or colitis. These drugs...
include ganciclovir, foscarnet (Foscavir), sulfa derivatives, and pentamidine (NebuPent, Pentam 300). Moreover, patients receiving chemotherapy for treatment of HIV-associated malignancies typically develop neutropenia. Irrespective of the cause of neutropenia, severe neutropenia complicated by a febrile episode should be evaluated aggressively for the development of bacteremia, as in the non-HIV-infected population [47].

### HIV-Related Coagulopathies

**"Lupus Anticoagulants"

Circulating inhibitors of coagulation are associated with diseases such as systemic lupus erythematosus, AIDS, and lymphoproliferative malignancies; certain drug therapies (eg, chlorpromazine); and intravenous drug use. These so-called lupus anticoagulants are acquired antibodies, either IgG or IgM, directed against proteins that bind phospholipids [48]. The presence of such an inhibitor is established by the use of phospholipid-dependent coagulation assays, such as the activated partial thromboplastin time (aPTT) or Russell viper venom time (RVV), or is confirmed on enzyme-linked immunoassay (ELISA), depending on the nature of the antibody [48]. Paradoxically, these lupus anticoagulants are associated with in vitro prolongation of the aPTT or RVV, but clinically, are associated with increased thrombosis in the non-HIV-infected individual. In patients with HIV infection, the presence of a lupus anticoagulant does not appear to increase the incidence of thrombosis [49]. The anticoagulant may manifest during HIV-related infections and often disappears with treatment of the infection [5,6]. If a patient has a prolonged aPTT with no history of bleeding, the presence of the lupus anticoagulant should be suspected. Invasive procedures may be performed in the presence of the lupus anticoagulant without increased bleeding risk [49].

### Microangiopathies

Microangiopathies, specifically, thrombotic thrombocytopenic purpura, have been described in patients with HIV infection [50-52]. Thrombotic thrombocytopenic purpura is a relatively rare disease characterized by fever, neurologic and renal abnormalities, purpura, microangiopathic hemolysis, and thrombocytopenia. Its exact pathogenesis is unknown. Vascular injury caused by immune complexes, endotoxin, or other causes of endothelial injury have been implicated, as have increased platelet agglutination and abnormally large circulating von Willebrand factor complexes. At present, it is unclear whether the occurrence of thrombotic thrombocytopenic purpura in HIV-infected individuals is related to circulating immune complexes or to immunoglobulin dysregulation associated with HIV disease. The mortality of this disease is high, as in the non-HIV-infected population, and therapy should include plasma transfusion and plasmapheresis.

### Bone Marrow Examination

Bone marrow biopsies are frequently performed to evaluate peripheral cytopenia or persistent fever in patients with HIV infection. Most patients demonstrate normocellular marrow elements, although abnormalities in maturation with dysmyelopoiesis (dysplasia), dyserythropoiesis, erythroid hypoplasia, megaloblástosis, and hemophagocytosis have been described (Figures 2, 3, and 4) [53-56]. Increased numbers of plasma cells and lymphoid aggregates composed of benign-appearing, well-differentiated lymphocytes are often noted (Figure 5) [5,57,58]. Marrow hypoplasia may manifest as serous atrophy, a condition characterized by marrow fat atrophy and deposition of gelatinous-type material, resulting in defective hematopoiesis (Figure 6) [59]. Myeloproliferative syndromes and leukemia are not more prevalent in this patient population [5,57]. For the most part, the marrow changes in asymptomatic HIV-infected patients appear nonspecific and offer little to the clinician in the way of diagnostic or prognostic clues. There are, however, certain conditions for which performing bone marrow aspiration, culture, and biopsy is indicated. Infiltrative disease of the bone marrow commonly contributes to the hematologic abnormalities seen in these patients. Infectious causes of infiltrative diseases include mycobacterial disease (both M avium complex and M tuberculosis), fungal disease (Histoplasma, Cryptococcus, and Cocciidioides infection), and, rarely, parasitic disease (Pneumocystis and Leishmania infection) (Figures 7, 8, and 9). Neoplastic infiltration is due primarily to lymphoma.

Infiltration of the bone marrow by M avium complex usually results in isolated anemia, whereas infiltrative disease of other causes typically manifests as pancytopenia. Constitutional symptoms associated with anemia and/or other cytopenias in the absence of a revealing work-up usually warrant a bone marrow examination to rule out lymphoma or an underlying opportunistic infection [60]. Evidence of Kaposi's sarcoma does not characteristically appear in the bone marrow aspirate or
biopsy specimen; however, lymphomatous involvement may be found. Granulomatous disease with a positive acid-fast bacillus stain suggests *M avium* complex or *M tuberculosis* infection, although well-formed granulomas may not be present. HIV-infected patients with both non-Hodgkin's and Hodgkin's lymphoma frequently have marrow involvement (Figure 10). Marrow examination is useful in these individuals not only for staging but also to assess the myeloid reserves before the initiation of cytotoxic chemotherapy. Patients with thrombocytopenia in the absence of anemia or leukopenia warrant bone marrow evaluation to ensure adequate megakaryocytes. In rare instances, diagnoses other than immune thrombocytopenic purpura may be established.

**Therapeutic Growth Factor Support**

Colony-stimulating factors (CSFs) play an integral role in the treatment of HIV-related cytopenias [61-68] (see Table 3). Theoretically, these agents could increase the number of target cells for HIV replication or enhance viral replication within target cells, leading to HIV disease progression [63]. In vitro studies have documented increased viral production in the presence of macrophage-CSF (M-CSF), granulocyte-macrophage-CSF (GM-CSF, sargramostim [Leukine]), and interleukin-3, but not granulocyte-CSF (G-CSF, filgrastim [Neupogen]) [23]. Clinical studies, however, have not documented an acceleration of HIV disease caused by the use of CSFs [62,64]. In several trials, neutropenic patients with AIDS responded to GM-CSF with a rapid increase in neutrophils and their precursors in conjunction with improved qualitative neutrophil functions [65,66]. Many chemotherapeutic trials now involve the administration of CSFs. Human recombinant erythropoietin (EpoGen, Procrit) has been administered to HIV-infected patients with anemia secondary to zidovudine therapy (Table 3). The best responses have been noted in patients with intrinsic erythropoietin levels < 500 mU/dL [5,62]. Some patients with higher erythropoietin levels may respond to such therapy [67], but use of erythropoietin in these individuals should be addressed on a case-by-case basis. The concomitant use of G-CSF or GM-CSF and erythropoietin may limit the hematologic toxicities caused by zidovudine therapy [68].

**References:**

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