Pathophysiology and Management of HIV-Associated Hematologic Disorders

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The human immunodeficiency virus (HIV) has been identified as the causal agent for the acquired immunodeficiency syndrome (AIDS). Infection with this virus has been associated with a broad range of clinical outcomes, particularly evident in the hematopoietic system. Impaired hematopoiesis, immune-mediated cytopenia, and altered coagulation parameters have been described following HIV infection. This review will discuss the clinical manifestations, postulated pathophysiology, and current therapeutic approaches to the hematologic abnormalities associated with HIV.

HEMATOPOIESIS

Clinical findings. Decreased blood cell counts are a common manifestation of HIV infection. In addition to the characteristic decrease in CD4-positive T lymphocytes, anemia occurs in approximately 70%, granulocytopenia in 50%, thrombocytopenia in 40%, and lymphopenia in 70% of AIDS patients.1-4 These abnormalities may be on the basis of accelerated destruction or underproduction of blood elements and are frequently multifactorial. Ineffective hematopoiesis may result from direct suppressive effects of HIV, opportunistic infection, or tumor infiltration in the marrow or antiretroviral, antimicrobial, or antitumor therapy. Discriminating among the multiple, possible etiologies of cytopenia may therefore be difficult.

In general, the incidence of low blood cell counts increases in frequency with progressive immunologic deterioration and advanced disease due to HIV. However, isolated cytopenia, particularly thrombocytopenia, may be the presenting manifestation of HIV infection unassociated with severe immune deterioration.5-11 HIV infection should therefore be considered in the differential diagnosis of any patient being evaluated for decreased blood counts. Major risk factors for HIV infection include homosexual or bisexual contact, heterosexual relations with a person at risk, intravenous (IV) drug use, receipt of blood products during the period of 1977 to 1985, and in the case of a child, a mother with risk factors.12

Evaluation of a patient with known HIV infection and an abnormal blood count should proceed along standard lines with particular attention to the recognized hematologic toxicity of intermittent therapy. Consideration must also be given to infections associated with AIDS that may result in either direct suppression of the bone marrow (BM) or in reticuloendothelial cell dysfunction. The most common of these infections are Mycobacterium avium intracellulare (MAI) and cytomegalovirus (CMV). Disseminated MAI results in increased BM reticulum, occasional granulomas, positive smears for acid-fast bacterium, and, less commonly, pseudo-Gaucher cells.2,13 Cytomegalovirus infection offers no pathognomonic findings upon morphological examination of the BM. Fungi, particularly Cryptococcus neoformans14 and Histoplasma capsulatum15 are other pathogens that may be found in the BM of these patients and that result in hematologic abnormalities. Discriminating between these processes and HIV in the etiology of low blood counts requires the directed search of a microbiology laboratory and careful follow-up of patients undergoing appropriate antimicrobial therapy. In addition to infections, Kaposi’s sarcoma and lymphoma should be evaluated as contributing processes. Kaposi’s sarcoma, although rarely directly involving the marrow, does frequently result in gastrointestinal (GI) lesions, which may be a source of blood loss. Lymphoma is generally aggressive and disseminated in AIDS patients and often involves the BM.16,17 The pathogenesis, diagnosis, and clinical management of malignancies associated with HIV have recently been reviewed.18

Even in the absence of an identifiable secondary cause for cytopenia, abnormalities of BM morphology are frequent following HIV infection.2A,19-22 Increased plasma cells and benign-appearing lymphoid aggregates are commonly seen. These may represent a physiologic response to unusual antigenic stimulation or dysregulated B-cell proliferation due to HIV. The cellularity of the BM is frequently increased, although hypocellularity has been observed in approximately 5% of patients.19 There is often an increase in eosinophils and a focal or diffuse increase in reticulin. Abnormalities in maturation are common with megaloblas-
tic changes, and occasionally ring sideroblasts are noted.\textsuperscript{22} Despite these morphological changes, an increase in the incidence of myeloproliferative syndromes or frank nonlymphocytic leukemias has not been reported.

**Mechanisms.** Several defects in hematopoiesis have been described in the setting of HIV infection. Ineffective production of mature circulating blood cells could be due to decreased numbers of marrow progenitors. Initial studies of in vitro BM progenitor colony formation from patients with HIV infection demonstrated that in the presence of HIV negative serum, CFU-GM and BFU-E were quantitatively and qualitatively similar when compared to HIV seronegative donor controls.\textsuperscript{24} However, using a different marrow culture system, reduced progenitor colony growth from patients with AIDS or AIDS-related complex (ARC) has been observed.\textsuperscript{25} In this latter study most of the patients were IV drug users, and the source of colony-stimulating factor (CSF) was phytohemagglutinin-leukocyte-conditioned medium (PHA-LCM) rather than recombinant growth factors. Reduced numbers of CFU-GM were seen in another study as well. In 70 of 78 patients using giant-cell tumor-conditioned medium as a source of CSF, reduced myeloid and erythroid progenitor proliferation was observed in all seropositive patients regardless of their degree of immunosuppression.\textsuperscript{26} Some patients had opportunistic infections, however, and were on potentially myelosuppressive antibiotics. Differences in study populations, possible intercurrent infectious pathogens, and culture techniques in these reports may account for the disparate results.

Recent studies have addressed whether HIV may directly infect BM progenitor cells and thereby induce phenotypic abnormalities of these cells. The retrovirus infects follicular dendritic cells and monocye-macrophages in vivo\textsuperscript{27-32} and cell lines of human B cells, monocytes, myeloblasts, and promyelocytes in vitro.\textsuperscript{28,30,32-37} BM from a seronegative donor could be infected in vitro with HIV and myeloid progenitor colonies derived from HIV-infected BM-released virus when cultured in vitro.\textsuperscript{24} Interpretation of these results, however, is complicated by the known infectibility of more mature cells of the monocyte lineage that could contaminate myeloid progenitor colonies grown in vitro. Recently Folks et al\textsuperscript{38} enriched for myeloid progenitor cells by selecting for the cell-surface marker My10 (CD34) and exposed these cells to HIV. Following prolonged in vitro culture, these cells were found to contain viral particles by electron microscopy, and reverse transcriptase activity was detected in the culture supernatant. Of note, this purified population of cells did not have detectable surface CD4, the primary receptor for HIV binding, raising the possibility of alternate portals of viral entry in myeloid progenitor cells. Similarly, there is controversy as to whether HIV may infect monocytes via receptors other than CD4, such as by binding in the presence of antibody to the phagocyte Fc receptor.\textsuperscript{39,40} Demonstrating direct infection of myeloid progenitors by HIV in vivo and examining the consequences of that infection requires further study.

In addition to the effects of HIV on marrow progenitors, hematopoiesis could be impaired by abnormal expression of hematopoietic growth factors. Cells comprising the BM environment, such as T lymphocytes, monocytes/macrophages, and stromal cells, are known to elaborate cytokines that may affect progenitor proliferation and differentiation. Among these, T cells and macrophages are infected in vivo with HIV. Whether endothelial and mesenchymal cells may also be infected is under investigation.\textsuperscript{35} Infection of BM accessory cells could result in altered production of hematopoietic growth-regulatory factors affecting blood-cell development within the BM compartment. Recent data indicate augmented expression of specific cytokines that may have effects on hematopoiesis, such as TNF and interleukin-1 (IL-1), in HIV-infected monocytoid cells.\textsuperscript{41}

In addition to altered expression of regulatory cytokines, HIV-infected accessory cells may exert inhibitory effects on BM cells. In one study, marrow colony production was enhanced by depletion of BM T cells in HIV-infected donors.\textsuperscript{26} T-cell–depleted marrow was then cocultured with increasing concentrations of circulating or marrow T cells. These results resulted in an inverse correlation of T cells with progenitor colony growth. No such changes in colony growth were seen with depletion or addition of monocytes, suggesting a T-cell–specific effect.

Independently, Leiderman and colleagues\textsuperscript{45} observed a significant decrease in CFU-GM upon cocultivation of AIDS BM mononuclear cells with normal peripheral blood progenitors. They postulated a soluble inhibitory factor derived from the infected patients' cells as the mechanism of this suppression. Media conditioned by the patients' cells contained a glycoprotein of 84 Kd that demonstrated inhibitory activity when purified. There was no reactivity of HIV immune sera with this purified protein, suggesting that the protein was not a product of the viral genome but rather a host protein produced in response to HIV infection.

Another series of experiments demonstrated circulating factors that may inhibit hematopoiesis following HIV infection.\textsuperscript{24} In the presence of serum containing antibodies to HIV, BM progenitor cultures from HIV-infected patients showed suppression of both granulocyte-macrophage colony-forming units (CFU-GM) and burst-forming units-erythroid (BFU-E). This effect was not seen in marrow cultures from seronegative donors. In addition, BM growth was evaluated in the presence of patients' serum prior to and after these patients had undergone seroconversion. While serum obtained before HIV infection had no effect on CFU-GM or BFU-E, serum obtained after HIV infection markedly suppressed in vitro myelopoiesis and erythropoiesis.

To define the inhibitory component of AIDS serum, the immunoglobulin fraction of the serum was purified. This fraction was shown to suppress CFU-GM and BFU-E formation. Similarly, rabbit heteroantisera raised against HIV envelope glycoprotein specifically suppressed CFU-GM. Anti-HIV antibodies were thereby implicated as the suppressing factors acting either directly against HIV-infected progenitor cells or via an indirect effect against infected marrow accessory cells. A number of different potential mechanisms for abnormal hematopoiesis following HIV infection have thus been defined. The relative importance of
each requires further study and refinement in laboratory methods to recreate the BM environment in vitro.

ANTIBODIES TO PERIPHERAL BLOOD CELLS IMMUNE-MEDIATED THROMBOCYTOPENIA

Clinical findings. The presence of thrombocytopenia in patients seropositive for HIV who are otherwise asymptomatic is not considered a criterion for advanced disease as defined by the Centers for Disease Control classification schema. Thrombocytopenia is not associated with an increased short-term risk of progression to AIDS when compared with nonthrombocytopenic seropositive persons. In one study at 37 months of follow-up, patients with thrombocytopenia had a 37% incidence of developing AIDS, not significantly different from HIV-infected individuals with normal platelet counts.

The etiology of thrombocytopenia in AIDS may be complex, including immune-mediated destruction, impaired hematopoiesis as noted above, toxic effects from medications, and syndromes mimicking the hemolytic uremic syndrome or thrombotic thrombocytopenic purpura. Most commonly, however, isolated thrombocytopenia is associated with normal or increased megakaryocytes in the BM and parallels the clinical syndrome of classic autoimmune thrombocytopenic purpura (AITP).

Mechanism. Elevated levels of platelet-bound immunoglobulin have been detected in patients with HIV infection and are probably relevant to the development of thrombocytopenia. However, the specific mechanism of platelet autoimmunity remains controversial. Conflicting evidence has been presented depending upon the population studied and the method of detection used.

Initial reports evaluating the mechanism of thrombocytopenia in homosexual males by Walsh et al identified circulating immune complexes capable of binding platelets in the serum of these patients. These complexes could not be demonstrated in patients with classic autoimmune thrombocytopenic purpura. In addition, increased platelet-bound IgG and complement were found in HIV-positive individuals when compared with patients with autoimmune thrombocytopenia. Analysis of the polyethylene glycol-precipitated serum-immune complexes and platelet eluates revealed abundant anti–HIV-1 reactivity without apparent platelet-associated HIV antigen. In addition, purified anti–HIV-1 (gp120) antibody did not bind platelets. However, antibodies against anti–HIV-1 antibodies could be detected. Thus specific antibody-antibody complexes may occur with HIV infection, bind to the platelet surface, and accelerate platelet destruction. Subsequent reports have defined anti-immunoglobulin antibodies in the serum of HIV-infected patients as reactive with F(ab')2 fragments of usually broad but occasionally limited specificity. Thus a subset of patients with elevated immune complexes and thrombocytopenia have anti-idiotypic antibodies. These have been seen in patients with other disorders of immune regulation, such as rheumatoid arthritis and systemic lupus erythematosus. Whether they are epiphenomena or are relevant to the pathophysiology of thrombocytopenia following HIV infection remains to be defined.

An alternative mechanism for low platelet counts has been offered by Stricker et al who studied thrombocytopenic, asymptomatic, seropositive male homosexuals and found antibody in 29 of 30 patients that was directed against a 25,000-Dalton platelet-associated antigen. Of note, this antibody cross-reacted with a 25,000-Dalton antigen associated with cultured cell lines infected with herpes simplex virus types I and II, suggesting the possible setting for its appearance. Since this antibody has been found in nonthrombocytopenic AIDS patients as well as thrombocytopenic patients, it is unclear as to its pathophysiologic role in inducing reduced platelet numbers. One postulated mechanism to account for differing clinical effects of both platelet-bound antibodies and immune complexes is abnormal Fc-receptor-mediated clearance described in AIDS. Some patients with antiplatelet antibodies may maintain higher platelet counts due to impairment of macrophage phagocytosis of blood elements.

ANTIBODIES TO ERYTHROCYTES AND GRANULOCYTES

Clinical findings. In addition to immune-mediated thrombocytopenia, an increased incidence of positive, direct, antiglobulin tests and antineutrophil antibodies have been reported in HIV-seropositive patients. Despite the presence of antibodies on RBCs, hemolytic anemia is rare in HIV-infected patients. The majority of anterythrocyte antibodies are not associated with hemolysis. The antibodies may be reactive with specific red cell antigens (anti-i is common) or due to the antiphospholipid antibodies documented in patients with HIV infection. Alternatively, Inada et al have shown deposition of circulating immune complexes on erythrocytes via the C3b receptor in HIV-infected patients. Using a direct antiglobulin test for IgG, IgM, and anti-C3b, 85% of patients with AIDS, 68% of patients with ARC, and 44% of the healthy homosexual group were positive. Another potential source of positive antiglobulin tests is the high rate of coexistent infections in this population that may be associated with anterythrocyte antibodies.

Using a granulocyte immunofluorescence test (GIFT), antibodies against neutrophils have been detected in ten of 34 male homosexuals, although only four of these ten patients were neutropenic. In a similar study, antibodies to neutrophil antigens were documented in 32% of AIDS patients. Therefore antibodies bound to blood-cell surfaces are common in AIDS patients, although their relationship to cytopenias is not direct.

Mechanism. The presence of anterythrocyte, antigranulocyte, and antiplatelet antibodies may be due to the general defect in regulation of antibody production characteristic of HIV infection. Several mechanisms have been proposed to explain this phenomenon, including abnormal B-cell regulation by HIV-infected T cells, direct activation of B cells by HIV or a B-cell response to coincident Epstein-Barr virus (EBV) or CMV infection. As with platelets, it is
unclear if the antibodies associated with the cells are due to nonspecific attachment or represent specific autoreactivity.

COAGULATION ABNORMALITIES ASSOCIATED WITH HIV INFECTION

Clinical findings. Antiphospholipid antibodies with characteristics of the lupus anticoagulant have been documented in patients with HIV. The prevalence of this finding has ranged from 20% to 70% in these studies. A prolonged, activated, partial thromboplastin time (aPTT) not corrected by addition of normal plasma and occasionally an increased prothrombin time (PT) are characteristic. The aPTT does not correct with prolonged incubation with Kaolin; diluted tissue thromboplastin prolongs the prothrombin time assay disproportionately; and the dilute Russell viper venom time is prolonged, all consistent with a lupuslike anticoagulant. One study characterized the causative antibody as being an IgM in six of seven patients. High titers of the associated anticardiolipin antibodies have been found in HIV-positive patients and are generally of the IgG type.

Unlike the clinical sequelae associated with antiphospholipid antibodies in other settings, deep venous thrombosis and pulmonary embolism have only rarely been reported in HIV-infected patients. This clinical discrepancy may indicate a difference in the nature of the HIV-associated lupus-like anticoagulant compared with lupus-like anticoagulants in other settings.

Mechanism. Like other antiphospholipid antibodies, the pathophysiologic basis for the development of these antibodies is incompletely understood. An association between active opportunistic infection and the development of a lupus-like anticoagulant has been suggested. In a group of 52 AIDS patients, Gold et al found 26 to have a lupus-like anticoagulant. Twenty-five of these 26 patients had active Pneumocystis carinii pneumonia. Prospectively, four patients in this study and one in another developed the anticoagulant when they developed an opportunistic infection (four with Pneumocystis pneumonia and one with MAI). Disappearance of the anticoagulant was noted in two patients following successful treatment of their pneumonia. Another study followed 25 nonhemophiliac AIDS patients prospectively for 6 months. Over that time, 13 of 25 patients developed a prolonged aPTT. However, only one of these patients had an active opportunistic infection. Similarly, other investigators have documented the presence of anticardiolipin antibodies in patients who are HIV seropositive and who do not have active opportunistic infection. Therefore, the association of lupus-like anticoagulant with intercurrent infection remains ill-defined.

In addition to lupus-like anticoagulants, some HIV-seropositive patients have been found to have qualitative abnormalities in platelet function. Specifically, prolonged bleeding times and abnormal aggregation to the agonists ADP, collagen, and epinephrine have been demonstrated. Based on dilution studies, this abnormality has been shown to be related to a serum factor. The nature of this factor is unclear and does not generally result in a clinically significant coagulopathy.

HEMATOLOGIC MANIFESTATIONS OF ANTI-HIV THERAPY

Clinical findings. The complex pathophysiologic mechanisms that may contribute to abnormal hematologic function in HIV infection may be further exacerbated by the agents used to treat HIV or complicating opportunistic infection. The antiretroviral agent, Zidovudine or Azidothymidine (AZT), has frequently been associated with myelosuppression. In the AZT Collaborative Working Group Study, BM suppression was common, with anemia (Hgb < 7.5/dL) occurring in 34% of AZT-treated patients following 6 weeks of therapy. Twenty-one percent of AZT-treated patients required multiple transfusions, compared with 4% of controls. In addition, among the AZT-treated patients, 16% developed neutropenia (less than 500 white cells/μL). Thrombocytopenia was less common, with 12% of AZT-treated patients experiencing a 50% reduction in their platelet numbers and only a single patient reaching less than 25,000 cells/μL. Indeed, there was a relative sparing of platelets, with mean platelet counts actually increasing at week 16 from 184,000 to 228,000/μL in AZT-treated patients as compared with 180,000 to 191,000 in controls. BM hypoplasia occurred in three patients with a limited ability to recover after drug withdrawal. In general, however, cytopenias do respond to the cessation or reduction of AZT. As might be expected, patients with more severe disease as evidenced by performance status, low CD4 numbers, and pre-existing cytopenias are more susceptible to the toxic side effects of AZT. In addition, a low serum vitamin B12 level (<200 pg/mL) has been identified as a risk factor for AZT-induced myelosuppression, although the pathophysiologic relationship of this finding to the toxicity is unclear. Concomitant use of acetaminophen, initially thought to be associated with increased BM toxicity, appears not to be independent of other factors linked to marrow suppression.

Other antiretroviral agents have also been documented to affect hematopoiesis. Suramin treatment resulted in granulocyte counts of less than 2,000 cells/μL in 26% of patients and thrombocytopenia in 12% of the same group. Trials with ribavirin have noted severe anemia requiring transfusion. Dideoxycytidine (ddC) has recently been shown to cause leukopenia, while dideoxycytidine (ddA) and its metabolite, dideoxyinosine (ddI), may be less myelotoxic reverse-transcriptase inhibitors and have recently entered clinical trial.

Other myelosuppressive drugs frequently used to treat the infectious complications of AIDS include ganciclovir (DHPG) for CMV infection, pentamidine or trimethoprim-sulfamethoxazole for Pneumocystis carinii pneumonia, pyrimethamine-sulfadiazine for CNS toxoplasmosis, and acyclovir for disseminated herpes simplex or herpes zoster. The myelotoxic effects of these agents are particularly common in AIDS patients.

Mechanisms. AZT is a nucleoside analogue that results in chain termination of reverse-transcriptase DNA synthesis and thereby inhibits retroviral replication. Although with far less efficiency, AZT may also inhibit cellular DNA polymerases and thus impair hematopoietic cell proliferation. In addition, intracellular pools of deoxycytidine are
diminished in the presence of AZT. The relative preservation of platelet numbers in treated patients suggests cell type-specific differences in AZT toxicity. These may reflect differential AZT uptake or metabolism (as has been seen with thymidine) resulting in megakaryocyte sparing. Alternatively, the antiretroviral benefit of AZT may be preferentially manifest in megakaryocyte development. Red cells are a common target of AZT therapy and may be selectively decreased. This phenomenon is associated with erythroid abnormalities of the BM (aplasia, hypoplasia, or maturation arrest) and does not correlate with either the increased MCV (seen in the majority of patients on AZT) or erythropoietin abnormalities. Indeed, erythropoietin levels are generally increased relative to anemic, non-AZT-treated controls, suggesting an abnormality of the erythroid precursors. Altered pyrimidine metabolism may again be relevant in this setting.

Although low levels of serum vitamin B12 have been documented in up to 20% of patients with AIDS, it is likely to be on the basis of altered cobalamin transport proteins rather than inadequate intake or absorption. Elevated cobalamin binding capacity has been seen in four of five seropositive patients with low serum B12 levels. This situation is similar to the low levels of serum B12 that may be found in multiple myeloma patients with increased transcobalamin II levels. Supplemental vitamin B12 has not altered the suppressive effects of AZT on the BM.

AZT is metabolized by hepatic glucuronidation; therefore other drugs that affect glucuronidation (such as probenecid) may also alter AZT metabolism and should be used with caution. Agents known to have myelosuppressive effects, including many of the drugs used to treat infections in AIDS patients, may be anticipated to potentiate AZT myelosuppression.

**THERAPEUTIC APPROACHES**

*Use of hematopoietic growth factors.* The presence of quantitative and qualitative abnormalities in leukocytes in HIV-infected patients and the responsiveness of HIV patient BM cultures to recombinant growth factors in vitro provided the rationale for the use of recombinant colony-stimulating factors (CSFs) in this setting. Neutropenic patients with AIDS or ARC responded to IV recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) in a phase I clinical trial. A rapid, dose-dependent response in leukocyte count was observed with increases in mature and immature neutrophils, eosinophils, and monocytes. No changes in circulating reticulocytes or platelet counts were found. Discontinuation of GM-CSF resulted in a decrease of circulating leukocytes to baseline within three to nine days. In two patients with prior neutrophil functional abnormalities (one in phagocytosis and one in intracellular killing), GM-CSF reversed the qualitative defect. Of note, no effect was demonstrated on the ability to culture HIV from the patients’ peripheral mononuclear cells.

A subsequent study by Mitsuyasu et al. has demonstrated that recombinant human GM-CSF can be administered by daily subcutaneous (SC) injection to leukopenic HIV-infected patients for prolonged periods of time with a similar restoration of myelopoiesis. A dose-dependent response in peak leukocyte count was again seen with no consistent effect on lymphoid cell numbers. Chronic administration over a 6-month period did not lead to tachyphylaxis, and no adverse effects of long-term administration were noted. In particular, there was no consistent modulation of the HIV core (p24) antigen marker of vireologic activity in this study. This is of particular importance given the conflicting in vitro effects of GM-CSF on HIV expression in monocyte-macrophages. Although HIV expression is suppressed by GM-CSF in the monocytoid cell line U937, several investigators have documented enhanced HIV production in primary monocytes as well as cell lines when exposed to GM-CSF.

Treatment with GM-CSF was generally well-tolerated. However, a flulike syndrome with myalgias, chills, fever, nausea, and headache commonly occurred. Local phlebitis in the IV-treated patients and erythema at the site of injection were also frequently observed. Mild abnormalities in liver function tests were less common and transient.

The common dose-limiting occurrence of myelosuppression with the single-approved antiretroviral agent AZT has led to the use of hematopoietic growth factors in this setting. In vitro, GM-CSF restores myeloid progenitor intracellular pools of deoxynucleotides and decreases the levels of phosphorylated AZT, resulting in a reduced toxic effect of AZT on BM colony formation. Preliminary data from a clinical trial combining AZT and GM-CSF indicates that GM-CSF can overcome the neutropenia of AZT therapy (J.D. Levine, personal communication, May 1989). Whether thrombocytopenia and constitutional symptoms may be increased by this combination is unclear. Granulocyte colony-stimulating factor (G-CSF) appears to be hematologically active in HIV patients and is also under study in combination with AZT. Erythropoietin has recently been shown to decrease transfusion requirements and to increase hemoglobin concentrations in AZT-treated patients when compared with placebo-treated controls (S. Rudnick, personal communication, May 1989). This effect was most consistent in those patients with erythropoietin levels less than 500 mU/dL.

Combinations of growth factors may be necessary to overcome the complex cytopenias associated with AIDS. The first such study using G-CSF and erythropoietin in AZT-treated patients is currently in progress. Other factors, such as interleukin-3 (IL-3), that act on earlier progenitors in the hierarchy of BM development will likely be used in this setting as they become available. The ultimate challenges for these agents will be to provide the BM support necessary for antiretroviral agents to achieve a maximal therapeutic benefit. In addition, data from these studies may further lend insight into the pathophysiologic mechanisms of retroviral-induced cytopenias. Effects of recombinant cytokines in this patient population may be distinct from those of other groups given their complex underlying abnormalities.

In addition to increasing cell numbers, another potential therapeutic role for GM-CSF has been provided by the observation that intracellular levels of AZT and phosphorylation of AZT to its active form are augmented in monocytes by the growth factor. Inhibition of HIV replication by AZT
is markedly potentiated by this combination. This in vitro effect requires clinical testing but offers a potentially important area of development.

**Thrombocytopenia.** Treatment for HIV-related thrombocytopenia remains an issue of some controversy. Use of standard approaches such as corticosteroids and/or splenectomy are complicated by at least a theoretic concern of increased immunosuppression. Corticosteroids have been used successfully to increase platelet counts. However, the response is, in general, short lived. There have been reports that chronic low-dose corticosteroids may be effective in maintaining adequate platelet counts in some patients.

Use of splenectomy has resulted in response rates of 67% and higher, and the procedure has been well-tolerated. Relapse of the thrombocytopenia occurs with a frequency comparable to that of non-HIV-infected immune thrombocytopenia patients. However, Barbui et al observed the development of AIDS in nine of 36 patients (25%) who underwent splenectomy following corticosteroids. Five of 65 patients (8%) who did not. These data are not adequate to conclude that splenectomy predisposes to further immune suppression due to the size of this study and the normal variability in progression from ARC to AIDS, but they do raise an issue of concern.

Other modalities used in the treatment of classic immune thrombocytopenia have met with variable success in the HIV-infected patient. IV gamma-globulin has been found to have a high response rate, with 88% of patients achieving platelet counts greater than 50,000/μL, presumably by altering reticuloendothelial clearance. This response is generally rapid, though of limited duration. It may be most useful in the preoperative setting or for episodes of acute bleeding. Anti-Rh(D) has also been used in the treatment of HIV-associated thrombocytopenia with nine of 12 patients responding. Readadministration of this therapy has been found to be similarly effective. Small numbers of patients have been treated with vincristine with limited success. Danazol has been used with only 2 of 18 patients responding. There is a recent report of a thrombocytopenic patient responding to interferon alpha-2a. Improvement in thrombocytopenia in patients receiving AZT has been reported from uncontrolled and controlled trials. As previously discussed, the mechanism of such a response is unclear, and larger studies investigating this observation are in progress.

**Guidelines for treatment of patients with HIV-associated thrombocytopenia are similar to other thrombocytopenic patients. In general, less than half of the HIV patients with low platelet counts will require some kind of intervention, while 10% to 20% may achieve a spontaneous remission. AZT followed by splenectomy and/or IV gammaglobulin are the preferred therapeutic modalities at our center.**

**CONCLUSIONS**

HIV infection has multiple hematologic manifestations with prominent abnormalities in hematopoiesis, immunohematology, and coagulation. The poorly understood but clinically apparent, limited marrow reserve present in these patients magnifies the myelosuppressive effect of coincident infections or pharmacologic therapy. Indeed, myelosuppression is the dose-limiting toxicity of AZT, the currently indicated treatment for HIV infection in AIDS or ARC patients. The use of hematopoietic growth factors in augmenting hematopoiesis offers promise for overcoming some of these clinical problems. Further studies of these growth factors should yield insights into the pathophysiologic mechanisms of the formation and fate of blood cells in viral diseases.

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