Hematologic Manifestations of HIV/AIDS

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Objectives

1. Review the physiology of normal hematopoiesis.
2. Review the pathogenesis of the hematological manifestations of human immunodeficiency virus (HIV).
3. Identify the clinical manifestations of altered hematopoiesis resulting from HIV infection.
4. Discuss relevant laboratory findings in anemia, neutropenia, and thrombocytopenia.
5. Establish care guidelines for children with HIV infection and altered hematopoiesis resulting in anemia, neutropenia, and thrombocytopenia.

Key Points

1. Altered hematopoiesis in patients with HIV can affect all cell lines (white blood cells, red blood cells, and platelets).
2. Anemia is multifactorial in HIV infection, with causes including opportunistic infection, myelosuppressive drugs, nutritional deficiencies, and the direct effects of HIV on bone marrow progenitors and stromal elements.
3. The primary risk for children with HIV/AIDS with neutropenia is the risk for overwhelming and life-threatening infection.
4. The primary cause of thrombocytopenia in children with HIV/AIDS is an idiopathic thrombocytopenic purpura syndrome secondary to a dysregulated immune system as a result of HIV infection.

Overview

Altered hematopoiesis (blood cell production) occurs in patients with HIV infection. This change affects all three cell lines (red blood cells, white blood cells, and platelets) that come from stem cells in the marrow. Consequently, HIV-infected children may suffer from anemia (lowered levels of red cells), neutropenia (lowered levels of white blood cells called neutrophils), thrombocytopenia (lowered levels of platelets), or any combination of these three. The causes of these conditions are varied and are not fully understood. Evidence shows that HIV infects the progenitor cells in the bone marrow, the hematopoietic stem cells (HSCs), and causes abnormal function. When HSCs cannot produce adequate hematopoietic growth factors (the substances that stimulate the production of blood cells in the bone marrow), decreased production of blood cells occurs. Also, antiretroviral treatment for HIV infection, opportunistic infections and their treatment, and chemotherapy for treatment of HIV-associated malignancies also cause altered hematopoiesis, which can contribute to the problem.

This chapter reviews normal hematopoiesis and the clinical manifestations of children with altered hematopoiesis, followed by a discussion of the causes of the different manifestations of altered hematopoiesis and their management and treatment.

Normal Hematopoiesis

To understand abnormal blood cell production, one must know how normal hematopoiesis occurs. To have normal hematopoiesis, the HSC must be present because it is the cell from which all blood cells will be derived during a person’s lifetime.

HSCs are situated in the bone marrow, spleen, liver, and peripheral blood. HSCs in the bone marrow produce almost all blood cells, whereas the other sites assist in times of undue stress. Only about 5% of the HSCs in the bone marrow are functioning at any one time, yet they can maintain the hematopoietic system for the lifetime of the person.

In addition to the stem cell, supportive cells, called stromal cells, must be present for normal hematopoiesis to occur. T lymphocytes, macrophages, endothelial cells, and fibroblasts help to produce the hematopoietic...
growth factors that are needed for production and differentiation of normal white blood cells in the bone marrow. Erythropoietin, produced in the kidney, and thrombopoietin, produced in the liver, are necessary for proliferation and production of red blood cells and platelets, respectively. The cells of the bone marrow grow in clumps known as colonies. Cells differentiate from the earliest progenitor cells, the HSCs, to progenitor cells of the different cell lineages, and these colonies then further mature toward becoming red blood cells, white blood cells (neutrophils, monocytes), and platelets. The progenitors of the red blood cells are in the erythroid lineage, whereas the white blood cells are derived from the granulocyte-macrophage colonies of progenitor cells, and finally the megakaryocytes of the bone marrow give rise to circulating platelets.

Alterations in hematopoiesis can lead to abnormalities in red cell, white cell, and platelet count in the peripheral blood. A decrease in the number of white cells is called leukopenia, and a decrease in the number of platelets is called thrombocytopenia. A decrease in the white blood cells known as neutrophils is called neutropenia. Anemia is a decrease in red cell number, hemoglobin, or hematocrit. Anemia is further classified by the size of the red cells in the peripheral blood as microcytic (smaller than normal), normocytic (normal), or macrocytic (larger than normal).

Clinical Manifestations of Altered Hematopoiesis

Children with alterations in hematopoiesis should have a comprehensive patient history, physical examination, complete blood count, and liver function tests. Children with anemia should also have a reticulocyte count, lactate dehydrogenase test, and Coombs’ test. A peripheral smear should be examined because it provides a great deal of information on cell morphology and can give clues to the cause of the alteration in hematopoiesis. Bone marrow aspiration and biopsy may be necessary to determine the cause. The following sections review the signs and symptoms of anemia, neutropenia, and thrombocytopenia.

Clinical Presentation of a Child with Anemia
- Pale conjunctivae or palmar creases, jaundice
- Fatigue or irritability
- Decreased ability to concentrate
- Headaches, dizziness
- Tachycardia, heart murmur
- Cold or discolored extremities
- Glossitis
- Nail bed deformities

Clinical Presentation of a Child with Neutropenia
- May be asymptomatic
- Fever
- Skin ulcerations or lesions
- Tachypnea, cough, wheezing, rales
- Stomatitis, dysphagia
- Abdominal pain, diarrhea
- Perirectal pain or fissure

Clinical Presentation of a Child with Thrombocytopenia
- Bruising, petechiae, purpura
- Epistaxis
- Gingival bleeding
- Hematuria
- Hematochezia

Pathogenesis of Hematological Manifestations of HIV Infection

Abnormalities of Bone Marrow

Bone marrow in HIV-infected children undergoes changes. The most common changes seen in morphology of the marrow architecture include decreased cellularity and myelodysplasia (abnormal change of the cellular structure) affecting the cells of the erythroid lineage and the megakaryocytes. Dysplastic changes of the granulocyte-macrophage lineage with arrest of maturation can occur in the marrow of children with HIV infection.

These changes impair growth of bone marrow cultures in vitro from patients with HIV infection. There is a decrease in the number of HSCs in the bone marrow of patients with HIV infection. Furthermore, HIV can directly infect the bone marrow stromal cells, leading to aberrations in their function. This development in turn leads to abnormal maturation of the different bone marrow cell lineages and may explain the preceding structural changes.

One can also observe drug-induced suppression of bone marrow in children with HIV infection. The most common cause is the antiretroviral drug zidovudine (AZT). This
drug inhibits the colony formation of stem cells as well as erythroid and granulocyte-macrophage progenitor cells. Other drugs can affect the bone marrow, and drugs used to treat opportunistic infections in HIV-infected children suppress the bone marrow. Acyclovir and ganciclovir used in the prevention and treatment of herpes simplex virus infection and cytomegalovirus (CMV) infection can both suppress the marrow. Trimethoprim-sulfamethoxazole used to prevent and treat Pneumocystis jirovecii pneumonia also suppresses the bone marrow. Finally, opportunistic infections can cause marrow suppression, particularly CMV, parvovirus B19, and Mycobacterium avium complex (MAC) infections.

One should consider the diagnosis of marrow suppression in any child with HIV infection when the blood count demonstrates a decrease in white cell (leukopenia), platelet (thrombocytopenia), or reticulocyte (immature red cells) count. One should consider the diagnosis of bone marrow dysfunction especially if there are decreases in more than one cell line. Many other factors can cause anemia, which when present alone is not as concerning for bone marrow suppression. Evaluating a child for marrow suppression requires bone marrow aspiration and biopsy, and the marrow should also be sent for mycobacterial stains and culture.

Treatment of bone marrow suppression is predicated on therapy for the underlying cause. In the child with HIV infection, optimization of antiretroviral therapy and decrease in the viral load alone is often effective in resolving the marrow suppression. Identification and treatment of opportunistic infections is also critical.

Anemia

Anemia is the most common hematological abnormality found in children with HIV infection. Indeed, anemia was the initial manifestation of HIV infection in about 10% of children in a recent study in Italy. The importance of finding and treating anemia in children with HIV infection is underscored by data from their study showing anemia to be an independent prognostic factor of mortality in children with HIV infection. The prognostic significance of anemia at baseline is statistically significant in multiple retrospective studies in adults in the United States and Europe both in the pre-highly active antiretroviral therapy (HAART) and HAART eras.

The etiology of anemia in children with HIV infection is multifactorial, and managing anemia can involve a variety of modalities (Table 1). HIV infection and its direct effects on HSCs and stromal elements can lead to anemia. Opportunistic infection and myelosuppressive drugs might also cause anemia. Furthermore, children with HIV infection often have abnormally low levels of iron and possibly cobalamin (vitamin B12), substances necessary for normal red blood cell production. Iron deficiency, the most common cause of anemia worldwide, is a frequent comorbid and treatable condition in children with HIV infection. The association of vitamin B12 is less clear: one study showed serum B12 levels to be low in only 20% of adults with HIV infection. Anemia due to iron deficiency is microcytic, and that due to B12 deficiency has associated changes in the neutrophils known as megaloblastic change.

Another well-known cause of anemia is pure red cell aplasia, caused by infection with parvovirus B19, and should be considered in children with HIV infection that have isolated anemia. Other marrow-suppressive infections such as CMV and MAC often affect the white cell lineage, first leading to neutropenia rather than anemia. Anemia of chronic infection as caused by these agents is normocytic.

Myelosuppressive drugs such as zidovudine and trimethoprim-sulfamethoxazole can also lead to anemia. The anemia associated with zidovudine treatment is macrocytic, and indeed the red cells may be macrocytic even without anemia. Some practitioners use this finding to assess adherence to zidovudine therapy.

Finally, anemia can be a result of red cell destruction, or hemolysis, as opposed to an aberration of production. Clinically significant hemolysis in patients with HIV infection is rare. However, in children with G6PD (glucose-6-phosphate dehydrogenase) deficiency, administering medications such as those commonly used in the prophylaxis and treatment of Pneumocystis jirovecii infection can lead to clinically significant hemolysis.

Table 1 shows the management and treatment of anemia in children with HIV infection. Although many approaches to the workup and management of anemia in children exist, the basic fundamentals include obtaining a complete blood count with red cell indices and a reticulocyte count where available. The formulation of a diagnosis is based on the size of red cells along with
the physiological reason (decrease in production or increase in destruction). So a common approach involves classifying anemia into macrocytic, normocytic, or (most commonly) microcytic, on the basis of mean cell volume. The reticulocyte count is 1%-2% in the presence of a normal hemoglobin value. In the presence of anemia, the corrected reticulocyte count can help distinguish between anemia due to decreased production (low corrected reticulocyte count) versus that due to increased destruction (elevated corrected reticulocyte count).

For macrocytic anemia in a child with HIV infection or on therapy, the most common cause is zidovudine toxicity. If a child is receiving zidovudine as part of his or her HAART regimen, the provider must recheck the dosing of zidovudine to ensure that it is not being overdosed. Furthermore, because there is a range of doses that can be used for zidovudine and still be therapeutically effective, one can consider decreasing the dose while remaining in that therapeutic range to alleviate the anemia. This approach was more commonly taken in the past with dosing every 6 h; today with twice-daily dosing it is commonly felt to be less of a problem, although to my knowledge there have been no unequivocal studies published demonstrating this commonly observed finding. Table 1 lists the other common causes of macrocytic anemia, along with their management.
Normocytic anemia is also common in children with HIV infection. In a child not on therapy, one can often find this development as a result of the chronic disease state. In this situation the most important therapy is to treat the HIV infection with HAART. If the child has severe anemia, with a hemoglobin level less than 7 g/dL, at presentation it may be necessary to omit zidovudine from the chosen regimen. In a child already on therapy, the chronic disease state is expected to play less of a role if the child’s HIV infection is well controlled. However, to my knowledge there are no unequivocal studies showing that a low viral load in the peripheral blood necessitates a lack of activity of HIV infection in the marrow microenvironment; nonetheless, a normocytic anemia should prompt further considerations in a child already on HAART with viral suppression. Table 1 lists some of the important causes of normocytic anemia.

A mixed nutritional problem of iron deficiency and folate or vitamin B12 deficiency can also lead to a normocytic anemia. In a developing, resource-poor country where nutritional problems are frequent, one should address this possibility with a trial of iron therapy (6 mg of elemental Fe/kg of body weight divided twice daily orally) along with folate (1 mg daily by mouth) for at least 1 month. Persistent normocytic anemia for a child on HAART warrants a bone marrow examination looking for a specific cause such as infiltrative disease or opportunistic infection of the marrow by MAC (Table 1).

Finally, the other possibility to consider in a child with normocytic anemia is a destructive process. In a child who has signs of hemolysis such as jaundice and splenomegaly, it is especially helpful for diagnosis to send a direct Coombs’ test and to prepare a peripheral smear for review. In a child with Coombs’ test-positive hemolysis, an immune-mediated hemolysis is of concern, and these children should receive transfusion therapy only in life-threatening situations because the transfused red blood cells will probably also be hemolyzed. The peripheral smear can be helpful in showing signs of hemolysis with red blood cell fragments, spherocytes (spherical red cells, normally donut shaped), or schistocytes (sometimes called helmet cells because of their shape). This approach can help to rapidly diagnose hemolytic anemia, and therefore a peripheral smear is strongly recommended whenever hemolytic anemia is a consideration.

The most common type of anemia worldwide is microcytic anemia as a result of iron deficiency. This development is particularly of concern in resource-poor settings where nutritional deficiencies abound. Iron therapy as described earlier is indicated. The health care provider must advise the patient and family to administer the iron supplementation without dairy products and preferably with a citrus product such as orange juice, or it can also be given with vitamin C. The duration of therapy is 6 weeks to 3 months depending on response. The hemoglobin level should start to rise within 2-4 weeks; however, one must treat long enough after normalization of the hemoglobin to replenish iron stores in the liver. Table 1 describes the other causes of microcytic anemia are described in Table 1, and once again a peripheral smear can be helpful in distinguishing both thalassemia and lead intoxication from iron deficiency.

**Leukopenia and Neutropenia**

A decrease in white blood cell count, leukopenia occurs in about one-third of children with untreated HIV infection with white counts less than 3000 cells/µL. Neutropenia is an absolute neutrophil count (ANC) of less than 1500 cells/µL and is observed in almost half of children with untreated HIV infection. The risk of serious bacterial infection increases when the ANC falls below 500 cells/µL. To calculate the ANC, multiply the total white blood cell count by the sum of the percentages of segmented neutrophils and bands. For a white blood cell count of 3,000 cells/µL, segmented neutrophils of 24%, and bands of 4%,

$$\text{ANC} = 3,000 \text{ cells/µL} \times 0.28 = 840 \text{ cells/µL}.$$  

Like anemia, neutropenia in children with HIV is caused by various factors. Decreased levels of the factor that stimulates production of white blood cells in the bone marrow (granulocyte colony-stimulating factor [G-CSF]) are present in some patients with HIV infection. A deficiency of G-CSF can lead to chronic neutropenia. As discussed earlier, HIV infection suppresses the bone marrow and affects the granulocyte-macrophage lineage, resulting in leukopenia and neutropenia. Furthermore, HIV infection can directly result in lymphopenia as the infection progresses, leading to a decrease in CD4+ lymphocytes.

A major cause of neutropenia in these patients is myelosuppressive medications. In the past when zidovudine was the only therapy available, a dose of
180 mg/m² of body surface area given every 6 h was associated with neutropenia in about half of children, resulting in an ANC count of less than 750 cells/µL. Even a dose of 100 mg/m² given every 6 h orally resulted in clinically significant neutropenia. However, other reverse transcriptase inhibitors do not cause clinically significant neutropenia. Other drugs that are commonly used in children with HIV infection that cause neutropenia include acyclovir, ganciclovir, and trimethoprim-sulfamethoxazole.

HIV infection in children increases circulating immunoglobulins as a result of abnormal stimulation of B lymphocytes. These increased immunoglobulins can be directed toward elements of the person’s body, called autoimmune antibodies. These autoimmune antibodies include antineutrophil antibodies, destroying neutrophils once they have matured in the bone marrow and have been released into the peripheral circulation. However, levels of antineutrophil antibodies are not necessarily associated with the degree of neutropenia, although this remains a potential mechanism of neutropenia in children with HIV infection.

As with other disorders discussed herein, optimizing antiretroviral therapy is always advised and starting therapy for a previously untreated patient is important. Nonetheless, treatment of neutropenia is generally geared toward preventing and treating serious bacterial infections that can result from severe neutropenia. However, one should consider a child with HIV infection and moderate neutropenia (ANC <1000) who is febrile for admission to the hospital. One should always admit a child with severe neutropenia (ANC <500) and fever to the hospital. One should draw blood cultures from all patients with febrile neutropenia blood cultures and should start the child on broad-spectrum IV antibiotics. Monitoring of the white blood cell count and ANC while the child is febrile is advised.

Using growth factors such as G-CSF to stimulate production of neutrophils has been tried, although it is not clear when this therapy should be initiated and what the long-term effects may be in a child with HIV infection. Another growth factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), has been associated with an increase in HIV replication and probably ought to be avoided. G-CSF, on the other hand, has not been associated with an increase in viral replication because it is more specific for neutrophil precursors. Nonetheless, judicious use of G-CSF (at doses of 5-10 µg/kg/day intravenously or subcutaneously) is advised because the long-term effects on the bone marrow and potential for the induction of malignancy in children with HIV infection are unknown. If G-CSF therapy is used, one must monitor the neutrophil count to assess the child’s response.

Finally, one must consider medication toxicity. In a child being treated with zidovudine, consider changing to another antiretroviral. Other medications that can lead to neutropenia, such as acyclovir or trimethoprim-sulfamethoxazole, must be evaluated for their need and discontinuation must be considered. However, when a child, for example, is being treated for Pneumocystis jirovecii pneumonia with trimethoprim-sulfamethoxazole, this drug will probably need to be continued and the...
neutropenia managed with meticulous hygiene and coverage with antibiotics.

**Thrombocytopenia**

Thrombocytopenia occurs often in patients with HIV infection and is the second most common hematological abnormality found in children with HIV infection. The cause is not clear, although studies suggest that the primary cause of thrombocytopenia in children with HIV infection is idiopathic thrombocytopenic purpura (ITP). This is an abnormal process in which an autoantibody targets and ultimately removes circulating platelets from the peripheral circulation as they travel through the spleen. These are cross-reacting antibodies that are directed toward HIV proteins, particularly gp120 and p-24. Also, some studies demonstrate a decreased production of platelets from the bone marrow. As discussed earlier, the effect of HIV infection on stromal cells in the marrow plays a role. However, the progenitor cell of platelets, the megakaryocyte, carries the CD4 receptor and thus HIV may directly infect these cells, resulting in their decrease and subsequently a decrease in platelet production. Also, infection can lead to thrombocytopenia, and the opportunistic infections seen in children with HIV infection are no exception.

Thrombocytopenia is associated with rapid progression of disease in patients with HIV infection. There is also an association between thrombocytopenia and mortality; one study showed a mortality rate of nearly 40% in children with HIV infection and thrombocytopenia. Furthermore, thrombocytopenia complicates treatment of HIV infection and associated malignancies because the medications used often affect the platelet level.

No clear guidelines for the treatment of thrombocytopenia in children with HIV infection exist. Indeed, this is a matter of ongoing research and frustration for professionals caring for children with HIV infection. Experts agree that initiation of HAART in children presenting with HIV infection and thrombocytopenia is critical. In these children, antiretroviral therapy often corrects the thrombocytopenia that is secondary to HIV infection alone. However, children with either persistent thrombocytopenia or thrombocytopenia later in the course of their illness do not respond as readily to HIV therapy.

Platelet transfusion is sometimes necessary in life-threatening situations or in children with active bleeding. However, the utility of transfusion therapy is limited in children with HIV infection when one considers the risks of long-term transfusion therapy and the pathogenesis of thrombocytopenia discussed earlier.

Therapies directed toward ITP, including intravenous immunoglobulin (1 g/kg) and corticosteroids (prednisone 2 mg/kg/day), are effective in increasing platelet counts in the short term; however, they often do not result in a sustained rise in platelet level. Another approach, using the anti-D preparation WinRho, effectively increases platelet levels; however, it is associated with a decrease in red cells—a potentially unacceptable and expected side effect of this intervention. Furthermore, there is an association with acute nephritis limiting its use in children with HIV infection. When the thrombocytopenia is felt to be secondary to an ITP process and the child is otherwise clinically well, splenectomy can (according to some data) be as safe in children with HIV infection as those without. However, only half of HIV-infected children so treated experience a long-term elevation, and with the long-term risk of spleen removal, this intervention is less attractive. Therapy using the growth factor thrombopoietin is still under investigation, and future research to identify other interventions will be necessary if we are to surmount this difficult problem.

**References**