HIV / HAART Related Haematological Disorders: Diagnosis and Management

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ABSTRACT

Haematological abnormalities are probably the commonest complications of infection with HIV. Over 65% of patients with HIV infection, at some point of the other, become anaemic. This anaemia is of varied aetiology and hence requires careful work-up. Similarly, thrombocytopenia including of immune origin is common and often an early manifestation of the disease. Although less commonly discussed, neutropenia also occurs in these patients.

Venous thromboembolism with or without antiphospholipid antibody syndrome has been reported in about 2% of HIV-infected patients. The haemophagocytic syndrome is another rare complication of HIV infection. Lastly, AIDS-related lymphoma including primary effusion lymphomas, Castleman's disease and Hodgkin's disease are also important and life-threatening complications.

Besides disease, antiretroviral drug therapy is also responsible for many haematological manifestations. Following is an account of these complications.

Haematological complications secondary to HIV infection include anaemia, neutropenia, thrombocytopenia, venous thrombo-embolism, haemophagocytic syndrome, AIDS-related lymphoma including primary effusion lymphoma, Castlemann's disease and rarely Hodgkin's disease and myeloma.

ANAEMIA[1-5]

Anaemia occurs in 60-95% of patients at sometime or the other.[1] The incidence increases with the clinical stages of disease. It is independent of CD4 count and viral load. Recovery from anaemia is associated with decreased risk of death. A wide range of aetiological factors are associated with anaemia (Table 1). After nutritional deficiencies, the most frequent cause includes anaemia of chronic disease associated with blunted erythropoietin response. Drug therapy for HIV infection and its subsequent complications result in anaemia. Zidovudine (AZT) is the most notorious culprit.[2] Severe anaemia with macrocytosis develops within weeks in most patients. Parvovirus B19 related infection often responds to multiple courses of intravenous immunoglobulin therapy. Refractory cases finally respond to HAART therapy which reconstitutes patient's humoral immunity resulting in clearance of the virus. *M. tuberculosis*, MAC and *Histoplasma capsulatum* produce anaemia by infiltrating the marrow.[3] *Leishmania donovani* infection in Bihar can produce similar problem. All these four disorders are diagnosed by bone marrow aspiration and biopsy.[3]

Surprisingly, autoimmune haemolytic anaemia is rare in patients with HIV infection. Only few cases have been reported. Despite haemolysis, reticulocytosis is often absent.[4] HIV-associated anaemia responds to erythropoietin therapy.[5] This treatment is preferred over intermittent blood transfusion which is associated with increased morbidity and mortality probably secondary to infections with CMV, hepatitis B, hepatitis C, HTLV I / II, parvovirus B19 as well as transfusion-associated immuno-suppression.[5] Interestingly, leuko-depletion provides no clinical benefits.

THROMBOCYTOPENIA[6-10]

Association between thrombocytopenia and HIV infection is well-known for over 20 years.[6] Table 2 gives a list of possible aetiologies.[7] The commonest cause is immune thrombocytopenic purpura (ITP). This occurs in 30% of patients with AIDS, however, it typically arises early in the course of HIV infection and can be seen before any other manifestation of AIDS. Unlike primary ITP, it is more frequently seen in men. The antibody is believed to be induced by HIV glycoprotein 120 which cross-reacts with platelet GPIIIa. These antibodies can be found even in a patient with normal platelet count. Platelet kinetic studies have shown shortened platelet survival as well as HIV-induced apoptosis of megakaryocytes. Zidovudine therapy has improved platelet count without changing platelet survival and this suggests improved production. Megakaryocytes are infected by HIV virus and HIV viral particles have been documented in the megakaryocytes by electron microscopy. HIV p24 antigen has also been documented in the megakaryocytes by immunohistochemical techniques while HIV RNA was detected

Table 1: Causes of anaemia in HIV infection

- Deficiency
  - Iron
  - Folate
  - Vitamin B_{12}
- Inadequate production
  - Drugs
    - Zidovudine
    - Trimethoprime-sulfamethoxazole
    - Amphotericin B
    - Ganciclovir
    - Dapsone
    - Delavirdine
  - Infection
    - HIV itself
    - Parvovirus B19
    - MAC
    - M. tuberculosis
    - Histoplasma capsulatum
    - CMV
  - Neoplasia
    - Non-Hodgkin's lymphoma
    - Multiple myeloma
    - Hodgkin's disease
    - Castlemann's disease
  - Miscellaneous
    - Anaemia of chronic disease
- Haemolysis
  - Autoimmune haemolytic anaemia
    - G6PD deficiency (drugs)
    - Thrombotic thrombocytopenic purpura
- Blood loss (GI tract)
  - Infections : CMV, Candida
  - Non-Hodgkin's lymphoma
  - Kaposi's sarcoma
- Hypersplenism
  - Infections
  - Haemophagocytosis
  - Lymphoma
  - Cirrhosis

Table 2: Causes of thrombocytopenia in HIV infection

- Decreased production
  - Drugs
    - Trimethoprim-sulfamethoxazole
    - Pentamidine
    - Pyrimethamine
    - Ganciclovir
    - Fluconazole
    - Alpha-interferon
    - Rifabutin
    - Clarithromycin
    - Didanosine
    - Amphotericin B
    - Indinavir
    - Ritonavir
    - Delavirdine
    - Nelfinavir
  - Deficiencies
    - Folate
    - Vitamin B_{12}
  - Infection
    - HIV
    - Parvovirus B_{19}
    - Mycobacterium avium complex (MAC)
    - Mycobacterium tuberculosis
    - Histoplasma capsulatum
  - Neoplasia
    - Non-Hodgkin's lymphoma
- Increased destruction / sequestration
  - Immune thrombocytopenic purpura
  - Thrombotic thrombocytopenic purpura
  - Hypersplenism
    - Infection
    - Haemophagocytosis
    - Cirrhosis
  - Drugs
    - Saquinavir
    - Interferon

using in situ hybridization studies. Treatment is unnecessary unless patient is symptomatic or platelet count drops below 30,000/cmm. Almost 20% of patients with HIV-associated thrombocytopenia undergo spontaneous remission. The most effective treatment is the use of HAART therapy, however, historical treatment with AZT alone was also effective.[8] Other modalities of treatment include corticosteroids, IVIG, IV anti-D therapy, splenectomy etc. None of these immunomodulatory treatments have shown any obvious increase in the risk of progression of HIV infection to symptomatic AIDS.[9]

Thrombotic thrombocytopenic purpura (TTP) is another well-documented complication of HIV infection. It was recorded in 1.5% of affected patients prior to introduction of HAART therapy.[10] It is possible that TTP is provoked by HIV-related endothelial cell perturbation. The role of CMV virus and *E. coli* O157: H7 toxin cannot be ruled out. Therapy consists of plasma exchange. It is unclear whether HAART therapy is helpful in prevention or treatment of TTP.[10]

NEUTROPENIA[11]

Causes of neutropenia in HIV infected patients are enlisted in Table 3.[11] Commonest of these include inhibition of granulopoiesis by HIV virus itself, marrow infiltration by infectious organisms or neoplasia, adverse drug effects, autoimmune neutropenia and hypersplenism.[11] Treatment includes antibiotics to control infection, use of G-CSF or GM-CSF to stimulate myelopoiesis and initiation of antiretroviral drug therapy together with withdrawal of potential offending drugs.[11]

VENOUS THROMBO-EMBOLISM (VTE)[12-15]

Venous thrombo-embolism occurs in 2% of HIV-infected patients.[12] Aetio-pathogenesis includes age over 45 years, advanced stages of HIV infection, presence of CMV or other opportunistic infections, hospitalisation (immobilization), treatment with Indinavir or Megestrol acetate. CMV infection promotes adhesion of neutrophils and platelets to the endothelium. It may

Table 3: Causes of neutropenia in HIV infection

- Decreased production
  - Drugs
    - Ganciclovir
    - Zidovudine
    - Trimethoprim-sulfamethoxazole
    - Pentamidine
    - Rifabutin
    - Antineoplastic chemotherapy
    - Dapsone
    - Amphotericin B
    - Ritonavir
    - Delavirdine
    - Nelfinavir
  - Deficiencies
    - Folate
    - Vitamin B_{12}
  - Infection
    - Human immunodeficiency virus (HIV)
    - Mycobacterium avium complex (MAC)
    - Mycobacterium tuberculosis
    - Histoplasma capsulatum
  - Neoplasia
    - Non-Hodgkin's lymphoma
    - Multiple myeloma
- Increased destruction / sequestration
  - Autoimmune neutropenia
  - Hypersplenism
    - Infection
    - Haemophagocytosis
    - Cirrhosis

also induce antiphospholipid antibodies, elevate levels of factor VIII and von Willebrand factor. Indinavir and Megestrol acetate probably induce acquired protein C resistance (APC-R).

Coexistence of malignancy, inflammation, autoimmune disorders and vascular damage secondary to intravenous catheters, intravenous drug administration or CMV infection are other responsible factors.[13] Antithrombin III (AT-III) deficiency can occur secondary to HIV nephropathy leading to urinary loss. Acquired protein S deficiency is detectable in 75% of HIV-infected subjects, especially with CD4 counts below 200/cmm resulting in overt thrombosis in 10%. The lupus anticoagulants are detected in 0-30% of subjects, depending upon the sensitivity of tests carried out as well as the characteristics of the patients. Anticardiolipin antibodies are detected in 40% - 80% of subjects. None of these are strongly related to overt VTE. However, there are publications relating them to transient ischaemic attacks, stroke, avascular necrosis of bones, skin necrosis and major arterial thrombosis affecting the limb vessels.[14,15]

HAEMOPHAGOCYTIC SYNDROME[16]

It is a rare complication of HIV infection. It is characterized by proliferation of histiocytes and phagocytosis of marrow blood cell precursors. It results in pancytopenia, fever, splenomegaly and lymphadenopathy.[16] It could be due to HIV infection itself or secondary to EB virus, CMV, herpes simplex virus, human herpes virus 8 (HHV-8), parvovirus B19 or even tuberculosis. It has also been noted secondary to T-cell non-Hodgkin's lymphoma and even Kaposi's sarcoma.[16]

AIDS-RELATED LYMPHOMA[17-20]

Lymphoma is a late manifestation of HIV infection. It usually occurs with significant immunosuppression associated with CD4 cell count below 200/cmm. Majority of patients have one or the other AIDS-defining illness.[17] The commonest lymphoma is high grade, diffuse, B-cell non-Hodgkin's lymphoma.[18] They usually present in advanced stages and are often extra-nodal including primary cerebral lymphoma. The relative risk of immunoblastic lymphoma is increased by 600-fold while that of diffuse large cell lymphoma is increased by 150-fold than that expected in the general population.[18] There is a definite but lesser increase in the incidence of low grade lymphoma, T-cell lymphoma, Hodgkin's disease and multiple myeloma.[18]

All of these are more common in men. Genetic factors in the host may be operative. Heterozygotes for the 32 deletion of the CCR5 coreceptor gene are statistically less likely to develop lymphoma, while those with SDF-1 mutations (3'A) are statistically more likely to develop lymphoma.[18]

HAART therapy has significantly reduced the incidence as well as mortality of AIDS-related lymphoma, however, the decline is not as profound as that seen in other AIDS-defining conditions.[19]

The factors associated with shorter survival in patients with AIDS lymphoma include CD4 cells <100/cmm, stage III or IV disease, age >35 years, history of I.V. drug abuse and elevated LDH. The International Prognostic Index (IPI) for aggressive lymphoma has also been validated in patients with AIDS-related lymphoma.[20]

Previous use of low-dose chemotherapy is gradually replaced by more efficacious standard dose regimen in combination with G-CSF / GM-CSF and HAART therapy.[20] Such combination has produced remarkable increase in survival rates. These protocols have produced outstanding rates of complete remission and long-term, disease-free survival. Addition of Rituximab to standard chemotherapy has not substantially improved response and survival among elderly patients.[21]

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