Autoimmune hemolytic anemia in a child with AIDS

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Abstract
Anemia in Human Immunodeficiency Virus (HIV) disease is a common problem, and associated with multiple etiologies. Autoimmune hemolytic anemia in HIV infected people is a rare disease and it is not frequently reported in medical literature. We report a seven year old child with HIV-Acquired Immunodeficiency syndrome (AIDS) who presented with autoimmune hemolytic anemia and will review literature of HIV-associated autoimmune hemolytic anemia.

Key words
HIV, autoimmune hemolytic anemia, antiretroviral therapy

Introduction
Pediatric mortality due to Human Immunodeficiency Virus (HIV) has declined remarkably from 40% in 2009 to 31% in 2013 due to the availability of improved antiretroviral therapy (ART). HIV associated anemia is a major burden on morbidity and mortality of patients. These children have poor over all prognosis, survival and poorer short-term virologic response to antiretroviral therapy. Many factors may be contributory for anemia in HIV infected children such as HIV itself, micronutrient deficiency, opportunistic infections, anemia of chronic disease and antiretroviral drugs. Autoimmune hemolytic anemia (AIHA) has rarely been described in HIV-infected children, which may be fatal. We are reporting a case of a seven year old child with Acquired-Immune Deficiency Syndrome (AIDS) who presented with severe anemia and positive direct and indirect coombs test. A review of HIV-associated AIHA with clinic-pathological features is presented here.

Case report
A one year old boy presented in in our clinic with cough and fever since 20 days, and positive maternal HIV infection. He was born by cesarean section at term and was breast-fed for one month. There was no history of blood products and he remained well prior to presentation. He achieved his developmental milestones on time. His father died a month ago due to AIDS. Initial evaluation in the child showed positive HIV antibody, CD4 count 374 cells/mm³ and HIV-I RNA 1.32x10⁵ copies/mm³. Rest of his workup was unremarkable. The child was started on ART containing lamivudine, zidovidune and nelfinavir.

During his treatment the patient had regular follow up, was on co-trimoxazole (Septran) prophylaxis, had recommended vaccinations, supplemental iron and multivitamins. He showed progressive clinical (weight gain) and immunologic (peak CD4 count 1046 cells/mm³ at 2 years) improvement over next few years. During course of next 3 years the patient developed some opportunistic infections including oral candidiasis and repeated diarrheal episodes. His nelfinavir was switched to nevirapine at age 3.5 years. At age 5.5 years the child presented with persistent fever and lymphadenopathy for 6 months, which settled after starting anti-tuberculous therapy that was given for nine months.

At 7 years he presented with weakness, fatigability and poor weight gain. On examination he had pallor, oral thrush, hepatomegaly with drop in CD4 count to 10 cells/mm³ and HIV viral load of 3x10⁴ copies/mm³. Further evaluation for HIV drug-resistance showed protease inhibitor mutations (L90M, L10F), reverse transcriptase mutations (M41L, A62V, M184V, D67N, L210W, T215Y and K219N) and non-nucleoside reverse transcriptase inhibitor mutations (K101Q, Y181I). This translates to high level resistant to nelfinavir, lamivudine, emtricitabine, delavirdine and nevirapine. Patient was switched to second line available ART regimen including efavirinz, lamivudine and lopinavir/ritonavir.

After a few months the child again presented with anorexia, pallor and lethargy. On examination he had severe pallor, jaundice and hepatosplenomegaly. Investigations showed hemoglobin of 4.2 g/dl, LDH 762 IU/L and positive Coombs test (direct and indirect). The peripheral blood picture showed very high reticulocyte of 75% (Figure 1a, 1b).

![Fig 1a & 1b. Reticulocytes shown on supra vital stain after 37°C incubation of blood.](image-url)
On basis of the examination and laboratory findings a diagnosis of HIV-associated AIHA was made. He was managed with packed red blood cell transfusions and prednisone 2 mg/kg/dose with ART discontinued for 7 days.

Child showed significant improvement with steroids with hemoglobin of 8.4 gm/dl and reticulocytes decreased to 50% in 2 weeks and improved to normal values after 4 weeks. The steroids were given for 2 weeks and then tapered over next 2 weeks. After no further evidence of hemolysis child was restarted on second line ART regimen. He had no further episodes of hemolysis. However he continued to remain unwell off and on over next few years with fevers, diarrheas, growth failure and falling CD4 to 10 cells/mm$^3$. He eventually expired at age of 10 years probably due to drug-resistant-HIV and opportunistic infections (tuberculosis, pneumonia, recurrent GE and fevers).

**Discussion**

The prevalence and etiologies of anemia in HIV-infected children may be diverse as shown in many studies. Anemia occurs in 20-70% of HIV-infected children especially those with AIDS. It is an independent risk factor for disease progression and death. A systemic review of anemia in children with HIV/AIDS in both western and tropical countries showed anemia incidence ranging from 0.41 to 0.44 per person-year. Mild (hemoglobin <11 gm/dl) and moderate (hemoglobin <9 gm/dl) anemia were more prevalent with HIV infection. There was limited data on more severe anemia (hemoglobin <7 or <5 g/dl). The review concluded that anemia is a very common complication of pediatric HIV infection and is associated with poor prognosis. A retrospective study of 248 HIV children from India showed an overall prevalence of anemia to be 66% with 8% having severe anemia (Hb<7 g/dL). It highlighted some independent risk factors such as age younger than 6 years, advance HIV disease stage, stunting, rural residence and co-infection with pulmonary tuberculosis. A recent adult series and literature review has shown that cases of AIHA occurred in HIV patients who are severely immunosuppressed.

The etiology of anemia in children with HIV infection is not entirely clear and may be multifactorial in origin. These factors can suppress the bone marrow, which then fails to produce an adequate number of red blood cells (RBCs). Patients with HIV infection often have lower than normal levels of vitamin B$_12$, folate and iron. Possible causes include decreased red cell production, nutritional deficiency of iron, folic acid and vitamin B$_12$. Opportunistic infections, HIV-associated nephropathy causing decrease production of endogenous erythropoietin, myelosuppression by drugs such as zidovudine or proinflammatory cytokines (IL-1 and TNF) or increased red cell destruction due to autoantibodies causing autoimmune hemolysis have been implicated as other causes. The HIV virus may infect the progenitor stem cell in bone marrow or causes it to function abnormally. Autoimmune diseases and autoantibodies may also develop at different stages of HIV infection.

Autoimmune antibodies in HIV infected children have rarely been reported. Literature shows very limited cases reported in children with HIV-associated AIHA. Literature shows one case report of severe AIHA and was associated with disseminated intravascular coagulation in a 5 months old infant. Another hospital based screening study for AIHA from Nigeria of 98 adult patients found a frequency of 3.06%. It suggested that all patients with HIV infection and anemia should be screened for AIHA before giving any blood transfusions to avoid fatal transfusion reactions. Autoantibodies may be a significant cause of anemia but reticulocytopenia may lead to the under diagnosis of AIHA in HIV infected patients.

The clinical presentation of AIHA in HIV infected patients is pallor, jaundice, dark urine, fever, splenomegaly, severe hemolytic anemia and positive direct and indirect coombs test. Differential diagnosis should include infections, RBC membrane or enzyme defects, malignancy, immunodeficiency, drugs and autoimmune diseases. Evaluation should include CBC, reticulocyte count, direct coombs test and peripheral smear to look for microspherocytosis.

In AIHA, including those with HIV infection, treatment is directed to reduce production and efficiency of antibodies with removal of possible offending cause(s) and treatment of underlying disease such as HIV infection. Corticosteroids and immunoglobulins are considered the first line treatment in AIHA with remission rates >60%. For refractory cases splenectomy or immunosuppressive drugs may be an option. Transfusion with washed RBCs or matched with donor’s cells may be used in severe cases. Prevention of anemia in HIV is recommended to decrease mortality. Use of transfusions, iron supplementation, epoetin alfa and other strategies are being advocated as well. However safety and efficacy data are needed for such interventions in HIV infected children.

**Conclusion**

AIHA may occur in a child with HIV infection. Physicians should do appropriate workup for underlying etiology and institute early therapy including steroids.

**References**


