Refractory Anaemia in an Immunocompromised Patient - What is it?

Dhiraj Bhattad*, Vrinda Kulkarni**, Abhay Bhave***, Meenakshi Balasubramanian#, Dnyaneshwar P Upase+, Santosh Khude*

Abstract
Anaemia is common among human immunodeficiency virus (HIV)-infected patients. It may be directly attributable to the virus or may be caused by opportunistic infections, neoplasms or drugs that cause either bone marrow suppression or haemolysis. Pure red cell aplasia (PRCA) is an uncommon haematological disorder that causes severe transfusion dependant anaemia. We report a 36 year-old female with HIV infection who developed anaemia which did not improve even after discontinuing the offending drug, namely Zidovudine. Routine investigations were unhelpful but her bone marrow study was consistent with pure red cell aplasia. She showed dramatic improvement with steroids with subsequent transfusion independence.

Introduction
Anaemia is quite frequent in HIV patients. It occurs due to multiple aetiologies, such as anaemia of chronic disease due to the virus, medication induced bone marrow suppression (e.g. zidovudine, trimethoprim-sulphamethoxazole, amphotericin, etc), medication-induced haemolysis (e.g. trimethoprim-sulphamethoxazole, dapsone), and infection-related hypoproduction (e.g. parvovirus B19, disseminated tuberculosis, histoplasmosis, Mycobacterium avium complex (MAC)).1,2 Highly active antiretroviral drugs (HAART) cause suppression of the bone marrow cell precursors, leading to bone marrow failure.2 One of the rare causes of anaemia includes pure red cell aplasia (PRCA), which selectively affects the erythroid bone marrow cells. PRCA has been most commonly associated with thymomas, autoimmune disorders and malignant diseases.3 Here we describe a HIV positive patient who developed PRCA which did not reverse even after discontinuing Zidovudine but which responded to steroids.

Case Report
36 year old widow, resident of Mumbai but native of Nepal, known HIV-positive since 3 years, was referred to our Haematology department in May 2010 in view of anaemia and thrombocytopenia. On presentation, she gave complaints of ringing in ears, easy fatigability, generalised weakness and breathlessness on exertion. She did not give history of any blood loss from any site. She consumed mixed diet. She was on Anti-retroviral therapy (HAART) since January 2010 comprising Zidovudine, Lamivudine and Nevirapine and was compliant with the same. Retrospectively, she gave past history of multiple blood transfusions approximately 2 PCV / month in her home town for symptomatic anaemia. She did not give any other significant past history like Tuberculosis. On examination, she was haemodynamically stable. She was pale but anicteric. She did not have any petechiae or purpura. Rest of the general as well as systemic examination was normal with no palpable organomegaly or lymphadenopathy or any infective foci.

Her old reports were suggestive of repeated anaemia with normal RBC indices, normal white cell (WBC) and differential count, but slightly reduced platelets. Her complete blood count on presentation to our department revealed Haemoglobin (Hb) 4.6 gm%, normal RBC indices, WBC count 3100 cells/cmm, Neutrophils 45%, Lymphocytes 50% Eosinophils 3%, Monocytes 2%, Platelets 120000 cells/cmm and Reticulocyte count 0.1% (Normal 0.5-1.5%). Her peripheral smear did not suggest any abnormality. Iron studies were normal. There was no evidence of gastrointestinal blood loss on routine stool examination. Her other investigations showed normal bilirubin (T. Bilirubin 0.7 mg%, normal being upto 1 mg%, Direct Bilirubin 0.3 mg%), no elevation of serum LDH (238 IU/L, Normal 200-400 IU/L) and normal liver enzymes. Direct and indirect Coomb’s test was negative ruling out immune haemolysis. Her serum Creatinine was 0.6 mg% (Normal upto 1 mg %). Her CD4 count was 224/ cmm. Her ELISA for Hepatitis B surface antigen and antibody for Hepatitis C virus were negative. Routine urine examination, Chest X-ray and Ultrasonography (USG) of abdomen were also non-contributory.

Initially, patient was suspected to have bone marrow suppression due to Zidovudine, which was changed to Stavudine. But the patient’s haemoglobin did not improve inspite
of stopping Zidovudine for more than 3 weeks. Instead the patient continued to need repeated packed cell transfusions. In view of no haemolysis or blood loss, we suspected a bone marrow production failure and hence a bone marrow examination was carried out. Bone marrow aspirate and trephine biopsy showed erythroid hypoplasia with adequate megakaryocytes and leucopoiesis (Figure 1) consistent with Pure red cell aplasia (PRCA). It did not show giant pronormoblasts.

Her chest X-ray did not show any mediastinal widening. USG of the chest also did not reveal any retrosternal mass, suggesting absence of thymoma. She was initiated on Tab Prednisolone 40 mg/day (1 mg/kg) and three weeks later her Hb improved to 8.4 gm%, which further rose to 12.9 gm% in another month. The reticulocyte count improved to 3%. Repeat bone marrow aspiration was not performed in the patient. Tab Prednisolone was gradually tapered. Hb further improved to 14 gm% 3 weeks later (Table 1).

**Discussion**

PRCA is an uncommon disorder. It is defined when anaemia is associated with normal leucocyte and platelet counts, with corrected reticulocyte count < 1% and with < 5% erythroid precursors in bone marrow, in the absence of haemolysis. It is usually associated with autoimmune states, thymoma, pregnancy, malignant diseases, etc. There are very few case reports of AIDS-associated PRCA in the literature. There are two mechanisms of PRCA in AIDS, the first being the autoimmune response as a consequence of immune-dysregulated status in AIDS and the second being the myelosuppressive effect of antiretroviral therapy. Although steroid use has been associated with a controversial issue of possibly enhancing infections like tuberculosis in an immunocompromised state, it is important for us to identify and treat this cause of anaemia i.e. PRCA or else patients would continue to get haematinics unnecessarily or transfused indefinitely, without eliminating the root cause. This would add to the patient’s cost burden along with risk of other viral or transfusion related infections or morbidity.

Our patient fulfilled the above-mentioned criteria for PRCA. Other common causes like nutritional deficiencies, blood loss and autoimmune haemolysis were ruled out by relevant investigations. At the time of diagnosis of PRCA, the patient was receiving Zidovudine and Lamivudine. These two drugs have been associated with PRCA. PRCA typically occurs within the first 3 months of therapy with Zidovudine or Lamivudine. HB usually improves in 2 to 3 weeks after stopping Zidovudine. There was no improvement in HB even after stopping Zidovudine for more than 3 weeks in our patient, indicating that it may not have been the cause of anaemia. On the contrary, the haemoglobin improved with steroids indicating autoimmune pathology.

India is demographically the second largest country in the world and also has the third largest number of people living with HIV/AIDS. As per the provisional HIV estimate of 2008-09, there are an estimated 22.7 lakh people living with HIV/AIDS in India. Anaemia on HAART has been reported in 23% of the Indian patients. There is a chance of HIV-infected patients on HAART suffering from anaemia because of PRCA. This may go unnoticed due to the lack of awareness among the treating physicians. Hence, we would like to emphasise that in all cases of HIV on HAART with anaemia where the cause of anaemia is not established and the patient requires repeated blood transfusions, bone marrow aspiration must be done for excluding PRCA.

**References**