Introduction

Anemia is a frequent occurrence in human immunodeficiency virus (HIV) patients (incidence 23% as reported by Kumaraswamy et al.[1]). It occurs due to multiple etiologies, such as anemia of chronic disease due to uncontrolled virus, medication induced myelosuppression or hemolysis and infection related hypo-production. ART causes myelosuppression leading to bone marrow failure. Pure red cell aplasia (PRCA) is a rare cause, which selectively affects the erythroid bone marrow cells. There have been very few reports of zidovudine (AZT)[1‑4] and lamivudine (3TC)[5,6] induced PRCA, of which two have been reported from India.[1,2]

Case Report

A 52-year-old male was diagnosed HIV-1 positive 5 months back in November 2012 while investigating for fever and weight loss. His baseline CD4 count was 50 and viral load 500,000 copies per ml. He was started incorrectly on two nucleoside reverse transcriptase inhibitors - AZT/3TC combination by his local practitioner.

After 4 months of therapy, the patient presented to us with a 1 month history of gradually progressive fatigue and 2 weeks history of exertional dyspnea progressing to dyspnea at rest. He denied any history of fever, chest pain, palpitations, or cough.

Examination revealed severe pallor, resting tachycardia, pitting pedal edema, and signs of hyperdynamic circulation. He was...
Our patient fulfilled the criteria for PRCA. In contrast, mean corpuscular volume (MCV) was 80-96 fl, MCH (27.5-33 pg/cell), MCHC (334-355 g/L), and RDW (13%). Erythrocyte count (×10^6/L) was 5.5, total leukocyte count (×10^9/L) was 228, and platelet count (×10^9/L) was 156. Investigations revealed a microcytic hypochromic anemia. For etiological diagnosis, a bone marrow aspiration and biopsy were performed. Aspiration revealed a marked paucity of erythroid precursors 3%, myeloid:erythroid ratio of 20:1, giant pronormoblasts with cytoplasmic protrusions and bone marrow biopsy showed a prominent erythropoietic cell line suppression. His serum erythropoietin (EPO) level was elevated - 750 IU/ml (normal - 100–250 IU/ml). Bone marrow microbiology for tuberculosis mycobacteria growth indicator tube, fungal culture, and parvovirus deoxyribose nucleic acid (DNA) polymerase chain reaction (PCR) were negative (to rule out opportunistic infection).

He was given supportive treatment with two packed red-cell transfusions. His ART regimen was changed to TDF/3TC/ Efavirenz, and AZT was stopped. His serial hemoglobin values after stopping AZT are shown in Table 3. He responded clinically and hematologically to AZT withdrawal. Since his new regimen consisted of 3TC, it was not the cause of his PRCA.

### Table 1: Serial complete blood count values over 4 months

| Lab investigations (SI units) | November 16, 2012 (baseline-at time of HIV diagnosis) | November 30, 2012 (15 days after HIV diagnosis) | March 12, 2013 (5 months later) |
|-------------------------------|-------------------------------------------------------|-------------------------------------------------|--------------------------------|
| Hb (140-175 g/L)              | 109                                                   | 112                                             | 22                             |
| MCV (80-96 fl)                |                                                       |                                                 | 72.3                           |
| MCH (27.5-33 pg/cell)         |                                                       |                                                 | 27                             |
| MCHC (334-355 g/L)            |                                                       |                                                 | 340                            |
| RDW (13%)                     |                                                       |                                                 | 13                             |
| Erythrocyte count (×10^6/L) (4.52-5.9) | 5.5                                                  | 4.4                                             | 6.5                             |
| Total leukocyte count (×10^9/L) (4.4-11.3) | 228                                                  | 156                                             | 250                            |

1. Hb: Hemoglobin; 2. MCV: Mean corpuscular volume; 3. MCH: Mean corpuscular hemoglobin; 4. MCHC: Mean corpuscular hemoglobin concentration; 5. RDW: Red blood cell distribution width.

### Table 2: Liver and renal function tests on admission

| Investigations (conventional units) | Values |
|-------------------------------------|--------|
| LDH (115-221 U/L)                   | 224    |
| SGPT/ALT (7-41 U/L)                 | 90     |
| SGOT/AST (12-38 U/L)                | 74     |
| Serum creatinine (0.6-1.2 mg/dL)    | 1.2    |
| Serum Na⁺/K⁺ (mEq/L)                | 135/4.1|
| DCT                                 | Negative|
| Serum haptoglobin (50-200 mg/dL)    | 191    |
| B12 levels (200-950 pg/ml)          | 950    |
| Stool occult blood                  | Negative|
| Peripheral smear for microscopy     | Mild hypochromasia, few elliptocytes, microcytes, anisocytosis |
| Reticulocyte count (%)              | 0.01   |

1. LDH: Lactate dehydrogenase; 2. SGPT/ALT: Serum glutamate pyruvate transaminase/aspartate transaminase; 3. SGOT/AST: Serum glutamate oxaloacetate transaminase/aspartate transaminase; 4. Na⁺: Sodium; 5. K⁺: Potassium; 6. DCT: Direct coombs test.

### Discussion

PRCA is an uncommon disorder. It is usually associated with autoimmune states, pregnancy, infections, etc. It is defined as anemia with normal leukocyte and platelet counts, corrected reticulocyte count <1% and <5% erythroid precursors in bone marrow in the absence of hemolysis.[10] Our patient fulfilled the above criteria. In the immunocompromised host, persistent parvovirus-B19 infection is manifested as PRCA and chronic normocytic anemia.[7] In contrast, mean corpuscular volume (MCV) is almost always increased in any patient on AZT, in fact, it is used as a marker of adherence even in patients without anemia,[8] hence the MCV serves as a rapid and easy differentiator of the two conditions. In parvovirus infection, the erythroid lineage is prominently affected; however, neutropenia and thrombocytopenia are also frequent. These manifestations are more common in HIV patients with more advanced immunodeficiency.

For diagnosis, investigations for parvovirus-B19 DNA in the serum or bone marrow is warranted as in acquired immune deficiency syndrome (AIDS) patients, parvovirus antibodies may be undetectable or show only weak IgM titers.[7]
Parvovirus-associated PRCA was ruled out in our patient as parvovirus DNA PCR was negative. Autoimmune hemolysis was unlikely in view of a negative Coombs test. At the time of diagnosis, our patient was receiving AZT and 3TC. Both have been associated with PRCA but in our case, we attributed this to AZT as stopping of this drug reversed the hematological abnormality even while 3TC was continued.

There are two mechanisms of PRCA in AIDS, first - an autoimmune response due to dysregulated immune status and second - a myelosuppressive effect of ART. The possible mechanisms for hematosuppression could be due to the synergistic action of AZT and 3TC. Most physicians believe that withdrawal of AZT + 3TC combination is enough, and that bone marrow examination is not mandatory.[1,2]

As per Balakrishnan et al., PRCA typically occurs within the first 3 months of therapy with AZT/3TC but, there are reports of AZT-induced PRCA occurring even after 4 years of treatment.[1] In our patient, this complication occurred 4 months after starting therapy.

Treatment with AZT is limited by major hematological toxicity. In a study, 12% of patient developed severe anemia within the first 3 months of AZT treatment. In half of these, MCV remained within the normal range. Bone marrow examination revealed PRCA in one-fourth of them. Anemia resolved on drug discontinuation and reappeared on rechallenge. As per Cohen et al., erythroid aplasia appears to be a major cause of anemia occurring within the first 3 months of treatment. The earliest sign is anemia with a stable or only a slight increase in the MCV.[1]

EPO levels in a patient with HIV and anemia are generally lower than expected for the degree of anemia and treatment with EPO results in the correction of anemia. An exception to this is patients with AZT-associated anemia in which EPO levels are high.[1] In our patient, the EPO levels were high favoring the diagnosis of AZT-associated PRCA.

**Conclusion**

AZT-associated PRCA generally appears within 3 months of starting therapy. It is a normocytic normochromic anemia which differentiates it from the usual macrocytic anemia produced by AZT. Since AZT is widely used in India, physicians should be cognizant of this complication as it is reversible with simple drug substitution.

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**Conflicts of interest**

There are no conflicts of interest.

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