Case Report

Refractory anemia in human immunodeficiency virus: Expect the unexpected

Sumeet Prakash Mirgh[1], Vikas A. Mishra[2], Virti D. Shah[3], Jehangir Soli Sorabjee[4]

[1]Department of Clinical Hematology, AIIMS, [3]Department of Neurology, Sir Ganga Ram Hospital, New Delhi, [2]Department of Cardiology, G.S.V.M. Medical College, Kanpur, Uttar Pradesh, [4]Department of Medicine, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra, India

Abstract

Pure red cell aplasia (PRCA) is an uncommon hematological disorder affecting selectively the erythroid cell lines. PRCA is defined as anemia with normal leukocyte and platelet counts, a corrected reticulocyte count <1%, <5% erythroid precursors in the bone marrow and an absence of hemolysis. We describe a case of Zidovudine (AZT) induced PRCA causing severe anemia in a patient taking antiretroviral therapy (ART) after 4 months of starting therapy and in whom all other causes were excluded. The hematological abnormalities resolved after AZT was replaced with tenofovir and the patient remained transfusion independent thereafter. A slowly progressive normocytic-normochromic anemia and reticulocytopenia, without leukopenia and thrombocytopenia in a patient, should raise the suspicion of PRCA. Search for underlying diseases, infections and drugs may help in the diagnosis and etiology of acquired PRCA. Elimination of potentially causative factors may induce complete recovery. AZT is a well-known cause of anemia and thus should be used with caution in the initiation of ART.

Keywords: Anemia, human immunodeficiency virus, mean corpuscular volume, zidovudine

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]

Address for correspondence: Dr. Sumeet Prakash Mirgh, 401, Jai Gurudev C.H.S., Plot No. 6, Sector No. 1, Sanpada, Navi Mumbai - 400 705, Maharashtra, India.
E-mail: drsumeetmirgh@gmail.com

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/2249-4863.197288

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

How to cite this article: Mirgh SP, Mishra VA, Shah VD, Sorabjee JS. Refractory anemia in human immunodeficiency virus: Expect the unexpected. J Family Med Prim Care 2016;5:727-9.

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
Erythrocyte count ($\times10^{12}$/L) (4.52-5.9)			0.8
Total leukocyte count ($\times10^{9}$/L) (4.4-11.3)	5.5	4.4	6.5
Platelet count ($\times10^{9}$/L) (172-450)	228	156	250

†Hb: Hemoglobin; ‡MCV: Mean corpuscular volume; §MCH: Mean corpuscular hemoglobin; ‖MCHC: Mean corpuscular hemoglobin concentration; ¶RDW: Red blood cell distribution width

hypoxic on room air confirmed by arterial blood gas (pH - 7.39, PO_2-68, PCO_2-30, HCO_3-25). Systemic examination revealed an ejection systolic murmur grade 3/6 in a pulmonary area with use of accessory muscles of respiration and mild nontender hepatomegaly.

He was investigated as shown in Table 1 (baseline investigations) and Table 2. Investigations revealed a microcytic hypochromic anemia with very low reticulocyte count. Iron studies and serum ferritin were normal. After workup, the differential diagnosis was thought to be either drug induced or secondary to an opportunistic infection (*Mycobacterium avium*-complex, parvovirus, fungal infections) or even possibly immune reconstitution inflammatory syndrome (IRIS). However, his repeat CD4 - 207 and viral load - 25,000 copies/ml were better which made the possibility of an opportunistic infection less likely. Similarly, the absence of fever, lymphadenopathy, any pulmonary infiltrates or uveitis ruled out the possibility of IRIS. The absence of macrocytosis pointed against the usual AZT-induced anemia. Hence, the possibility of PRCA secondary to drugs – AZT/3TC was considered.

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 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

†LDH: Lactate dehydrogenase; ‡SGPT/ALT: Serum glutamate pyruvate transaminase/alanine transaminase; §SGOT/AST: Serum glutamate oxaloacetate transaminase/aspartate transaminase; ‖Na^{+}: Sodium; ¶K^{+}: Potassium; 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.[1] 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]

Table 3: Serial investigations after zidovudine discontinuation

Lab investigations (SI units and normal values)	2 weeks after discontinuation	4 weeks after discontinuation	6 weeks after discontinuation	10 weeks after discontinuation
Hb† (140-175 g/L)	45	77	90	101
MCV‡ (80-96.1 fl)	79	80	82	80
Total leukocyte count ($\times 10^9$/L) (4.52-5.90)	5.5			
Platelet count ($\times 10^9$/L) (172-450)	230	250		
Reticulocyte count (%)				
CD4 count (on TDF/3TC/EFV regimen)				356

†Hb: Hemoglobin; ‡MCV: Mean corpuscular volume. TDF: Tenofovir disoproxil fumarate; 3TC: Lamivudine; EFV: Efavirenz

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[2] 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.[3]

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.[9] 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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Balakrishnan A, Valsalan R, Sheshadri S, Pandit VR, Medep V, Agrawal RK. Zidovudine-induced reversible pure red cell aplasia. Indian J Pharmacol 2010;42:189-91.
2. Bhattad D, Kulkarni V, Bhave A, Balasubramanian M, Upase DP, Khude S. Refractory anaemia in an immunocompromised patient – What is it? J Assoc Physicians India 2013;61:673-5.
3. Cohen H, Williams I, Matthey F, Miller RF, Machin SJ, Weller IV. Reversible zidovudine-induced pure red-cell aplasia. AIDS 1989;3:177-8.
4. Hassan A, Babadoko AA, Mamman AI, Ahmed SA. Zidovudine induced pure red cell aplasia: A case report. Niger J Med 2009;18:332-3.
5. Nakamura K, Tateyama M, Tasato D, Haranaga S, Tamayose M, Yara S, *et al.* Pure red cell aplasia induced by lamivudine without the influence of zidovudine in a patient infected with human immunodeficiency virus. Intern Med 2014;53:1705-8.
6. John MA, Rhemtula YA, Menezes CN, Grobusch MP. Lamivudine-induced red cell aplasia. J Med Microbiol 2008;57(Pt 8):1032-5.
7. Florea AV, Ionescu DN, Melhem MF. Parvovirus B19 infection in the immunocompromised host. Arch Pathol Lab Med 2007;131:799-804.
8. Romanelli F, Empey K, Pomeroy C. Macrocytosis as an indicator of medication (zidovudine) adherence in patients with HIV infection. AIDS Patient Care STDS 2002;16:405-11.
9. Fauci AS, Lane HC. Human immunodeficiency virus disease: AIDS and related disorders. In: Longo D, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, *et al.*, editors. Harrison's Textbook of Internal Medicine. 18th ed.. New York: McGraw-Hill; 2012. p. 1506-87.