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Chronic Parvovirus B19 Infection and Pure Red Cell Aplasia In A PLHIV Patient

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ABSTRACT

Pure red cell aplasia (PRCA) is a bone marrow failure disorder where only the red cell lineage is getting affected. It manifests as normocytic, normochromic anemia or macrocytic anemia with reticulocytopenia with absent or extremely infrequent erythroid precursors in the bone marrow. We have both congenital and acquired causes. Human immunodeficiency virus (HIV) comes under a roof of family called Human Retroviruses (retroviridae). Globally, there is a burden of approximately 39 million people affected by HIV, with around 3.14 million residing in India. This accounts for approximately 0.7% of individuals aged between 15 and 49 years worldwide living with HIV. Within this population, approximately 0.6 million HIV-related deaths occur. HIV induces an immunocompromised state, serving as fertile ground for infections that can be treated and prevented by appropriate ART regimens. The most common hematological manifestation in HIV infection is anemia, which increases mortality and morbidity in these patients. Therefore, identifying a correctable cause is crucial when treating People Living with HIV (PLHIV). One such treatable cause is anemia due to pure red cell aplasia caused by Chronic Parvovirus B19 infection. Treatment options include steroids, appropriate ART, and Intravenous Immunoglobulin (IVIG). Here, we discuss the case of an 18-year-old boy, a PLHIV patient who presented to us with refractory anemia and its successful treatment with Intravenous Immunoglobulin.

Keywords: Human immunodeficiency virus (HIV); Pure red cell aplasia (PRCA)

BACKGROUND

Pure Red Cell Aplasia (PRCA) manifests as normocytic, normochromic, or macrocytic anemia with reticulocytopenia and a scarcity of marrow erythroid precursors. PRCA can be associated with constitutional, primary, and secondary causes. One of the most common acquired causes is Parvovirus B19 infection. Parvovirus

B19, a small non-enveloped single-stranded DNA virus belonging to the Parvoviridae family, Parvovirinae subfamily, and Erythrovirus genus, infects humans, triggering the development of IgG antibodies. However, its effects are more severe in immunocompromised hosts such as those with HIV. HIV-induced immunosuppression creates an fertile ground conducive to various infections, with Parvovirus being no exception. In HIV patients, Parvovirus infection tends to become chronic, resulting in refractory anemia that does not respond to routine management, often necessitating recurrent blood transfusions.

CASE REPORT

An 18-year-old teenage boy, known to be living with HIV (PLHIV), presented to the outpatient department (OPD) complaining of breathlessness (NYHA class 2), easy fatigability, and palpitations for the past 2 months. He had a history of recurrent hospital visits and admissions for similar complaints in the past and had been found to have anemia, necessitating multiple blood transfusions. Diagnosed with HIV in 2017, likely through vertical transmission as both his father and brother are PLHIV patients, his initial CD4 count was 67, and he was started on a ZLE regimen. In June 2020, he developed severe anemia (Hb-3.8g/dl), leading to multiple blood transfusions. Due to non-compliance with ART, he experienced immunological and virological failure. Consequently, considering the ART failure and persistent refractory anemia, his regimen was changed to lopinavir/rtv abacavir and lamivudine since June 2020. He was then again admitted this time with similar illness for which further evaluation done and found to have following findings;

Table 1: Basic Laboratory Investigation

PARAMETERS	DAY 1	DAY 3	DAY 5
Hemoglobin	3.8 g/dl	4.5 g/dl	6.7g/dl
RBC	1.1 × 10^6/microL	1.8× 10^6/microL	3.1×10^6/microL
MCV	99 fL	98 fL	95 fL
MCHC	18 g/dl	19 g/dl	20 g/dl
MCH	34 pg	35 pg	36 pg
RDW CV	18%	18%	19%
Total count	2700	2800	2700
Neutrophil	57%	58%	54%
Lymphocyte	38%	36%	37%
Platelet	181000	1,90,000	2,10,000
Total bilirubin	0.2 mg/dl		0.3 mg/dl
Direct bilirubin	0.12 mg/dl		0.2 mg/dl
SGOT/SGPT	29/27 IU/L		22/26 IU/L
ALP	141 IU/L		137 IU/L
LDH	514 IU/L		480 IU/L

Urea	22 mg/dl		18 mg/dl
Creatinine	0.5 mg/dl		0.4 mg/dl
S.ferritin	597 ng/ml		
S.folic acid	11.9 ng/ml		
Vitamin B12	519 pg/ml		
Total protein	8 g/dl		
S albumin	3.4 g/dl		

Peripheral smear: normocytic normochromic anemia with reticulocytopenia (reticulocyte production index-0.1%), no parasites.

USG abdomen and pelvis- no organomegaly

Blood c/s and urine c/s – no growth

Bone marrow c/s, CBNAAT – negative

CT chest and CT abdomen – Normal study

Viral markers - CMV,EBV,HBV,HCV- negative

In view of refractory anemia and reticulocytopenia bone marrow aspiration and biopsy done.

Bone marrow aspiration- cellular marrow with marked erythroid hypoplasia and maturation arrest suggestive of pure red call aplasia

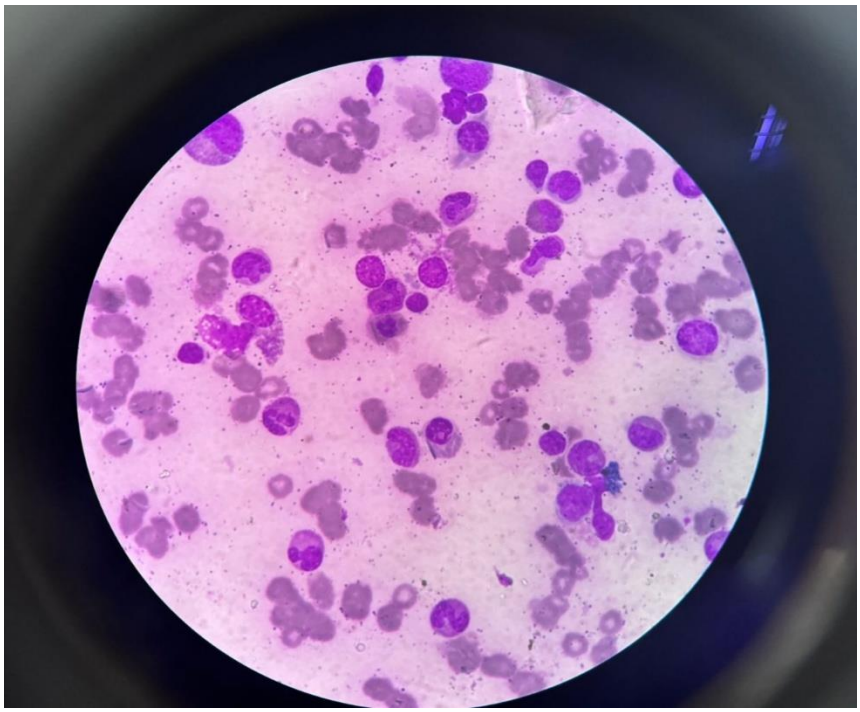

Figure 1: Bone Marrow Aspirate

Bone marrow biopsy – cellular marrow with marked decrease in mature erythroids and erythroid precursors with prominent intranuclear eosinophilic inclusions and peripheral chromatin condensation . suspicious of parvovirus infection.

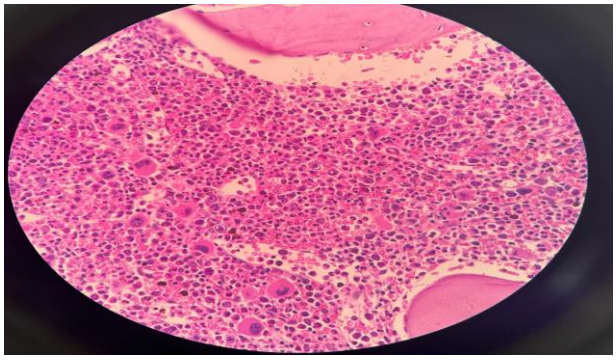

Figure 2: Bone Marrow Biopsy

Parvovirus B19 positive in serum and bone marrow(7).

The patient was subsequently diagnosed with Chronic Parvovirus-induced pure red cell aplasia and was initiated on a low dose of oral Prednisolone along with blood transfusions. Despite follow-up over six months, the anemia persisted and proved refractory to oral steroids and transfusions. Due to this persistent refractory status, the patient underwent treatment with IVIG at a dose of 400mg/kg for 5 days, with no observed transfusion reactions. Following this, the patient was discharged with a low dose of oral Prednisolone (5mg OD), and the ART regimen was changed to TLD. Currently, the patient remains asymptomatic and continues with regular follow-up.

Follow up report

Table 2: Follow Up Complete Bllod Count

PARAMETERS	FOLLOW UP
Hemoglobin	12.1 g/dl
RBC	4.18 × 10^6/microL
MCV	91 fL
MCH	28 pg
MCHC	31 g/dl
RDW	17%
Total WBC count	6.14× 10^3/microL
Neutrophil	36%
Lymphocyte	56%
Monocyte	5%

DISCUSSION

Human immunodeficiency virus (HIV) comes under a roof of family called human retroviruses(retroviridae). Globally, there is a burden of approximately 39 million people affected by HIV, with around 3.14 million residing in India. This accounts for approximately 0.7% of individuals aged between 15 and 49 years worldwide living with HIV. Within this population, approximately 0.6 million HIV-related deaths occur.[1] Among those infected, HIV related deaths occur in about 0.6 million people. HIV, as an immunocompromised state, provides fertile ground for infections that can be treated and prevented with the appropriate ART regimen. Pure Red Cell Aplasia (PRCA) is a bone marrow failure disorder characterized by the selective impairment of one single cell type. Causes for PRCA includes the following (7)

Table 3: Causes of Prca

CAUSES OF PRCA
CONSTITUTINAL
Diamond- Blackfan anemia
PRIMARY
Immune(T-cell autoimmunity)
Large granular lymphocytosis(LGL)(T-cell clonal expansion)
Transient erythroblastopenia of Childhood
SECONDARY
Autoimmune/collagen vascular disorders ○ Systemic lupus erythematosus ○ Rheumatoid arthritis ○ Inflammatory bowel disease
Lymphoproliferative malignancies ○ Chronic lymphocytic leukemia ○ LGL leukemia ○ Hodgkin's disease ○ Non Hodgkin's lymphoma ○ Angioimmunoblastic lymphadenopathy ○ Multiple myeloma ○ Waldenstrom macroglobulinemia
Other hematological malignancies ○ Chronic myelogenous leukemia ○ Chronic myelomonocytic leukemia ○ Myelofibrosis with myeloid metaplasia ○ Essential thrombocythemia ○ Acute lymphocytic leukemia
Solid tumors

○ Thymoma ○ Gastric cancer ○ Breast cancer ○ Biliary cancer ○ Lung cancer ○ Renal cell carcinoma ○ Carcinoma of unknown primary site
Infections Parvovirus B19 ○ Transient aplastic crisis of hemolytic anemia(acute infection) ○ Chronic PRCA(persistent infection due to immunodeficiency) ○ Hydrops fetalis (infection in utero) Other viruses ○ HIV ○ T-cell leukemia -lymphoma virus ○ Infectious mononucleosis ○ Viral hepatitis(A,B,C and E) ○ CMV Bacterial infections ○ Group C streptococcus ○ Tuberculosis ○ Bacterial sepsis
Drugs and toxins • Anti EPO antibodies(erythropoietin treatment)
Immunologic ○ Post allogenic transplant(donor isoagglutinins) ○ Pyoderma gangrenous
Others ○ Pregnancy ○ Riboflavin deficiency

One of the most common acquired causes of PRCA is Parvovirus infection (PB19). In hemolytic patients, this infection leads to temporary aplastic crisis. In immunocompetent individuals, it typically manifests as a benign childhood exanthem, while in adults, it can present as polyarthralgia/arthritis syndrome, resolving within 1-2 weeks via humoral immune response. However, in cases where an effective humoral response is absent due to

defective cellular immunity, the infection persists, leading to PRCA. In individuals with immunodeficiency, the virus can enter a chronic infectious phase. Upon entering the body, the virus binds to the P antigen in red blood cells (RBCs) and multiplies. Interestingly, some individuals lack this P antigen, rendering them inherently resistant to this infection.

HIV represents an immunodeficient state and serves as fertile ground for the development of infections. Therefore, individuals with HIV should be on Highly Active Antiretroviral Therapy (HAART) to prevent AIDS-defining opportunistic infections and maintain their CD4 count. A decline in CD4 count is often associated with an increased risk of opportunistic infections and malignancies. Anemia is the most common hematological manifestation in HIV, significantly impacting morbidity and mortality. Some authors suggest a correlation between the incidence of anemia and the progression of HIV, similar to AIDS-defining opportunistic infections and CD4 count. Thus, it's crucial to identify correctable causes of anemia in HIV patients. Historically, Parvovirus B19 has been implicated in 15% of severe anemia cases in these patients, particularly as the infection progresses into a persistent chronic phase. Chronic parvovirus infection represents one of the treatable causes of anemia, underscoring the importance of ruling it out during diagnosis.

For Diagnosis of pure red cell aplasia(9) ,we need

- Anemia presenting as normocytic normochromic or macrocytic
- Reticulocyte count below 10,000/microL (<0.5% of total red blood cells)
- Normal white blood cell (WBC) and platelet counts, excluding concurrent conditions like Chronic Lymphocytic Leukemia (CLL)
- Bone marrow with normal cellularity, containing less than 1% erythroblasts or less than 5% combined proerythroblasts and basophilic erythroblasts
- Absence of significant abnormalities in myeloid, lymphocytic, or megakaryocytic lineages, except in cases of concurrent CLL or Chronic Myeloid Leukemia (CML) diagnosis.

Diagnosis of chronic parvovirus infection leading to Pure red cell aplasia is made using these criteria(10):

- Characteristics in bone marrow indicative of PB19 infection,
- Detection of parvovirus DNA through serum PCR testing,
- Investigation to exclude alternative causes of PRCA.
- PRCA manifests as normocytic normochromic or macrocytic anemia, along with reduced reticulocyte levels and a scarcity of marrow erythroid precursors such as giant pronormoblasts.

PRCA induced by Chronic Parvovirus B19 (PB19) infection is typically treated using IVIG and other immunosuppressant drugs. No specific immunosuppressant has been found to be superior to others. In our patient's case, IVIG was administered at a dose of 2g/kg/day for 3 days. This IVIG formulation contains IgG antibodies targeting the VP1 and VP2 proteins of the viral capsid. Following IVIG treatment, the patient was discharged with oral Prednisolone at a dose of 5mg once daily and was scheduled for regular outpatient follow-ups. It's crucial for patients during this period to maintain good compliance with HAART, as a low CD4 count is associated with

frequent relapses that may necessitate maintenance IVIG therapy. Additionally, maintaining a CD4 count above 300 is essential to sustain remission and reduce the need for ongoing maintenance therapy.

CONCLUSION

Anemia in HIV infection requires identification and appropriate treatment due to its significant morbidity and mortality implications. Chronic parvovirus-induced pure red cell aplasia is a treatable condition, emphasizing the importance of its identification. Maintaining adherence to HAART in all HIV patients is crucial to prevent further complications.

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