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Warm Autoimmune Hemolytic Anemia in a Newly Diagnosed Patient with HIV: A Rare Hematological Complication

Dr. Swati Saini[1], Dr. Anushka Garg[2], Dr. Aryan Deol[3], Dr. Sheetal Panjariya[4], Dr. Darab Singh[5]

Abstract

Introduction: Autoimmune hemolytic anemia (AIHA) represents a relatively rare but important hematological complication among individuals infected with human immunodeficiency virus (HIV). Although anemia is the commonest hematological abnormality in this population, the immune-mediated causes, such as warm AIHA, tend to be overlooked. HIV-related immune dysregulation, polyclonal B cell activation, and immune reconstitution in response to antiretroviral therapy have all been implicated in the pathogenesis of AIHA.

Case Presentation: Here we describe a case of warm AIHA in a 36-year-old male with newly diagnosed HIV who developed this condition two months following initiation of tenofovir, lamivudine, and dolutegravir (TLD) combination therapy for his HIV infection. The patient had presentation of altered mental status, cognitive dysfunction, and severe anemia (hemoglobin level 3.6 g/dL) with macrocytosis (MCV 145 fL), profound reticulocytosis (43.1%), indirect hyperbilirubinemia, and elevated lactate dehydrogenase (2704 U/L). The peripheral blood film showed spherocytes, nucleated red blood cells, and polychromasia. The direct antiglobulin test was strongly positive (4+) for IgG and C3d, confirming warm AIHA. In addition, cerebrospinal fluid analysis and contrast MRI brain confirmed the diagnosis of Progressive Multifocal Leukoencephalopathy (PML) caused by infection with the JC virus. The management included blood transfusion, intravenous methylprednisolone (500 mg daily for three days) followed by high-dose oral prednisolone (60 mg/day), along with continuation of antiretroviral therapy. At discharge, hemoglobin had improved to 7.4 g/dL with clinical stabilization.

Conclusion: In this particular case, we learn about the need for a consideration of AIHA being one of the causes of severe anemia in newly diagnosed patients with HIV, especially in those who have been initiated on ART. Prompt treatment with corticosteroids along with continued ART is necessary to achieve good results. The occurrence of PML in this patient makes the situation even more complex.

Introduction

Anemia is one of the commonest hematological disorders seen in people living with HIV (PLHIV), with multiple etiologies that include chronic illnesses, malnutrition, bone marrow suppression, and many opportunistic infections [1]. Nevertheless, autoimmune hemolytic anemia is quite rare and underrecognized as a cause of anemia in PLHIV. It results from the formation of autoantibodies that target antigens on the surface of the red blood cells, leading to their early destruction. Autoimmune hemolytic anemia presents with anemia, increased reticulocyte counts, indirect hyperbilirubinemia, and high lactate

dehydrogenase levels [2].

The most common type of AIHA, which is called warm AIHA, has autoantibodies of the type IgG that stay active at body temperature; confirmation of this disease is done by means of a direct antiglobulin test (DAT) [2]. AIHA may be initiated by HIV/AIDS because the virus can stimulate autoantibody formation by means of mechanisms like molecular mimicry, while also causing an imbalance in immunity that makes people more vulnerable to autoimmune disorders. With respect to HIV infection, AIHA occurs at a later stage of the disease and carries a mortality rate of about 11%. [3]

Here, we present a case of warm AIHA in a newly diagnosed HIV-positive male who developed severe anemia shortly after initiating antiretroviral therapy. This case underscores the importance of considering immune-mediated causes in the differential diagnosis of anemia in PLHIV, especially when presenting with hemolytic features.

Case Presentation

A 36-year-old male, a resident of Nainital and working as a receptionist in Delhi, with no known comorbidities, presented with a history of forgetfulness for two months and altered mental status for the past one week. Cognitive impairment included amnesia for names, places, and the inability to memorize new facts. The modified sensory system comprised hypoactive delirium, irritability, paucity of speech, and disturbed sleep pattern. Weight loss was substantial during the same period, but there were no signs of fever, cough, vomiting, seizures, or altered bowel movements.

The patient was a known case of HIV, diagnosed 2 months back, and started on antiretroviral therapy including Tenofovir, Lamivudine, and Dolutegravir (TLD).

Examination findings include confusion regarding time, place, and identity. The patient was malnourished, anemic, and exhibited generalized maculopapular desquamation rash. Icterus was mild. Vital signs were normal. Systemic examination revealed diffuse abdominal tenderness without hepatosplenomegaly or ascites. The neurological examination showed a GCS score of 13/15 (E4V4M5), without focal deficits or meningism. Reflexes were hyperactive on both sides. Cranial nerve examination was within normal limits.

Initial investigations indicated severe anemia with hemoglobin levels of 3.6 g/dL and macrocytosis (MCV 145 fL). Reticulocytosis was high (43.1%). Anisopoikilocytosis, polychromasia, presence of nucleated red blood cells, and spherocytes were visible on the peripheral smear. Perpheral smear image is shown in Figure *1*.

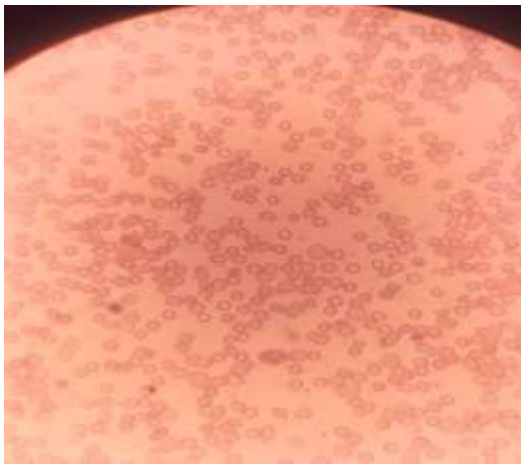

Figure 1: Peripheral smear showing RBC agglutination/clumping, anisopoikilocytosis, polychromasia, and scattered spherocytes

The LDH was very high (2704 U/L) along with indirect hyperbilirubinemia (Total bilirubin- 5.75 mg/dl, Indirect- 4.49 mg/dl). Results for the Antinuclear Antibody (ANA) test were negative. Direct Coombs Test result was very positive (4+) with monospecific tests showing positivity for both IgG and C3d. Baseline investigations are shown in Table *1*.

Investigation	Values
Hemoglobin	3.6 g/dL
MCV	145 fL
Reticulocyte count	43.13%,
TLC	18.36 × 10^3/µL
DLC	N/L/M/E: 82/13/1
Platelet count	374 × 10^3/µL
Peripheral smear	RBC agglutination with anisopoikilocytosis, macrocytic RBCs, polychromatophils, target cells, nucleated RBCs and spherocytes
Total bilirubin	5.75 mg/dL
Indirect bilirubin	4.49 mg/dL
LDH	2704 U/L
Direct antiglobulin test / Direct Coombs test	Positive, 4+
Indirect antiglobulin test	Positive, 2+
Monospecific Coombs test	IgG 4+, C3d 4+
Serum iron	156 µg/dL
Ferritin	2170 ng/mL
TIBC	242 mg/dL
Transferrin saturation	64%
Vitamin B12	1292 pg/mL
Folate	12.86 ng/mL

Table 1: Baseline investigations

N: Neutrophils
L: Lymphocytes
M: Monocytes
E: Eosinophils

Transfusion with 3 units of packed red blood cells was done. Hematology opinion was sought, and pulse corticosteroid therapy with intravenous methylprednisolone 500 mg for three days was initiated, followed by high-dose oral prednisolone (60 mg/day). Folic acid and other supportive treatments were given.

To evaluate his neurocognitive decline, cerebrospinal fluid analysis was performed, which was unremarkable except for PCR positivity for JC virus (18740 IU/mL). Contrast-enhanced MRI of the brain confirmed the diagnosis of Progressive Multifocal Leukoencephalopathy. A conservative approach was

taken, and ART was continued. Additional workup for opportunistic infections (toxoplasma, CMV, stool culture, and fundoscopy) was negative.

At discharge, the patient had stabilized symptomatically, and his hemoglobin had improved to 7.4 g/dL with no further drop observed during the hospital stay. He continued to receive oral corticosteroids, hematinics, and nutritional support. ART was continued without modification.

Discussion

India still carries a considerable load of HIV/AIDS, as per NACO's India HIV Estimations 2023 survey, which suggests that there are nearly 2.5 million people affected by the disease in India. Even though there is a fairly low prevalence rate of around 0.2%, India comes third in the world regarding the sheer size of its HIV epidemic, mainly because of the huge population in the country.

When considering hematological problems found in PLHIVs, anemia is the most commonly found disorder, and the presence of this problem has been associated with the fast progression of the disease and even with mortality risks. In the global setting, based on the available scientific data, it is known that about 46.6% of HIV-infected individuals suffer from this health problem. In the case of India, a wider prevalence rate of anemia has been found in the population infected with HIV, from 47% to 86%. [4]

Autoimmune hemolytic anemia is relatively rare, but it can be considered clinically relevant when it causes anemia in PLHIV. According to the current literature, the overall prevalence of the disease in the general population is about 1.77 cases per 100,000 people per year, and warm AIHA accounts for the majority of cases (~65% of all cases) [5]. It is assumed that the disease incidence is much higher in immunocompromised patients. In the case of PLHIV, the incidence of AIHA reaches 3.06%. [6]

The mechanisms underlying AIHA development in the setting of HIV infection are intricate and arise from multiple contributing factors. HIV infection leads to polyclonal B-cell activation, dysregulation of CD4+ T-cell immunity, and defective immune surveillance, all of which may contribute to autoantibody production. [7] Molecular mimicry between HIV antigens and host red blood cell antigens has also been proposed as a mechanism triggering autoimmunity. Research performed by Yen et al. (2017) indicated that patients infected with HIV who were being treated with HAART were at a higher risk of experiencing AIHA than those who were not on HAART [8]. This is due to immune reconstitution caused by antiretroviral therapy. However, our case is unusual, as AIHA occurred just two months after HIV diagnosis and shortly after ART initiation, suggesting a possible immune reconstitution inflammatory syndrome (IRIS)-like phenomenon- although IRIS typically presents with infectious symptoms.

A study by Jogdand et al. (2021) described two cases of AIHA in HIV-infected individuals, both of whom responded well to corticosteroid therapy. [3] Corticosteroids remain the first-line treatment for warm AIHA, with most patients responding to high-dose oral prednisolone (1 mg/kg/day). [9] In cases refractory to steroids or those requiring steroid-sparing strategies, options include Rituximab, Azathioprine, ciclosporin, or splenectomy. [9] In our patient, a 3-day course of intravenous methylprednisolone followed by high-dose oral prednisolone resulted in hemoglobin stabilization and symptom improvement, highlighting the efficacy of early immunosuppression.

Importantly, our patient had an abnormal mental state and was confirmed to have Progressive Multifocal Leukoencephalopathy because of the JC virus infection. This was managed in a conservative manner, but posed the issue of managing two conditions in the same PLHIV who were just confirmed: autoimmune and opportunistic infections. It is essential to highlight the fact that although neurological signs and symptoms do not occur in AIHA, the patient was concurrently found to have PML.

AIHA may present or become apparent after the initiation of ART and may be associated with immune recovery. Thus, physicians should always suspect any form of immune-mediated cytopenias early during the course of treatment.

Conclusions

The above case illustrates the significance of keeping AIHA in mind while diagnosing anemia among newly detected HIV patients. Timely detection, early administration of corticosteroid medications, and continuous ART have resulted in a positive outcome in this patient. Considering the possibility of coexisting problems among PLHIV, a multidisciplinary team approach is always recommended for proper treatment.

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