A Newly Diagnosed of Advanced HIV Diseases with Severe Anemia: A Case Report and Literature Review

Luh Ayu Made Paramita Dwisari Putri[a*], Gede Arya Dwipayana[b]

[a]*dwisarisariputri273@gmail.com*
[ab]*Department of Internal Medicine, Garba Med General Hospital, Badung 80363, Bali, Indonesia*

Abstract

Introduction: Human immunodeficiency virus (HIV) is an infection that attacks the body's immune system. The progressive immunodeficiency caused by the decrease of $CD4^+$, is responsible for the installation of Advanced HIV disease (AHD). Anemia is the most common hematological complications in HIV patients, that has impact on quality of life, morbidity, and mortality.

Case Report: A 37-year male patient was admitted in hospital with major complains of weakness and general malaise for 5 months before admission. The patient had history of multisexual partner. Physical examination showed the general appearance look moderate ill, each conjunctiva was pale, gingivitis, gum bleeding, oral plaque, and papular eruption on upper and lower extremity. Laboratory test was showed markedly severe anaemia with haemoglobin count of 5.4 g/dL. Anti-HIV rapid test was reactive. $CD4^+$ count showed 10 cell/mm^3. We assess the patient with Severe Anaemia, Stage 4 HIV infection pre highly active antiretroviral therapy, Wasting Syndrome, Pancytopenia caused by viral infection, Pruritic Papular Eruption, and Oral Candidiasis. The patient was treated by 4 bag packed red cell transfusion, Fluconazole 150 mg, and Cotrimoxazole 960 mg once daily.

Conclusion: Anemia is the most common hematological complications in HIV patients. Anemia may be encountered as the initial presentation of asymptomatic HIV infection, physicians should be alert to the possibility of HIV infection in every case of anemia. Early diagnosis and treatment of HIV also can help managed the anaemia. Management of anemia in HIV patients depends on the underlying cause.

Keywords: Anemia in HIV, Advanced HIV Disease, AIDS

1. Introduction

Human immunodeficiency virus (HIV) is an infection that attacks the body's immune system. HIV is a retrovirus that causes a multi-systemic disease within the action on cells that express $CD4^+$ protein in their cytoplasmic membrane. The progressive immunodeficiency caused by the decrease of $CD4^+$ T lymphocytes during HIV infection, is responsible for the installation of Acquired immunodeficiency syndrome (AIDS) or Advanced HIV disease (AHD), that is the most advanced stage of the diseases. It also can leading the individual to a predisposition to opportunistic infections and a lower quality of life. Data from World Health Organization (WHO) shows approximately 38 million individuals suffer from HIV worldwide at the end of 2021 with 1,5 million people becoming newly infected with HIV globally and 650.000 people of the was died from HIV-related cause.[1,2]

Hematological changes are one of the most common complications among people living with HIV/AIDS, occurring in approximately 30% of patients with an asymptomatic infection and in as many as 75–80% of those with AIDS.[3] Anemia is the most common hematological complications in HIV patients, and has a significant impact on quality of life, morbidity, and mortality. The virus, immune dysregulation, opportunistic infections,

and medications in HIV patients result in anemia.[4] The prevalence of anemia in persons with AIDS has been estimated to be 63% to 95%, making it more common than thrombocytopenia or leukopenia.[5]

According to WHO guideline, the diagnosis of anemia is based on concentration of hemoglobin, specifically when it falls below cut-off values; 12.0 g/dL for women and 13.5 g/dL for men. Low concentrations of hemoglobin are a frequent complication of HIV infections, and its occurrence is associated with increased morbidity and mortality.[6] Anemia in HIV infected individuals has multifactorial etiologies that make etiologic diagnostic challenging.[2] Several causes of anemia have been reported in HIV patients, among which the most commonly reported are deficiencies in minerals, such as iron, folat and vitamin B_{12}. In recent epidemiological studies, anemia has appeared to be the most common clinical burden in people living with HIV/AIDS, and its severity increases with declining $CD4^+$ count and progression of the HIV/AIDS to the AHD. Moreover, among those HIV patient with anemia influences the natural history of the disease, leading to disease progression, and is an independent predictor of death, irrespective of $CD4^+$ count or viral load.[4]

2. Case Report

A 37-year male patient from Bali ethnic was admitted in hospital with major complains of weakness and general malaise since 5 month before admission. The patient felt weak continuously throughout the day and felt disturbing when he did daily activities. The weakness getting better when he took a rest and getting worse during the activities. The patient also complaining about weight loss and gum bleeding for 4 months before admission. He did not know how much weight that he had lost, but he felt look thinner even though his appetite was normal. The patient also complaining about white spots in his mouth, sore throat, joint pain, also felt itchy and redness on his arm and lower leg. Prolong fever, diarrhea, nausea and vomiting was denied. He had no history of any chronic diseases such as heart diseases, hypertension, diabetes mellitus, kidney, lung diseases, liver diseases, or contagious infectious disease such as tuberculosis and HIV. He is already married and had history of multisexual partner. He did not mention any history of chronic diseases in his family and no history of smoking, drunk alcohol, use of intravenous drugs, blood transfusion, and consume herbal medication, nutritional supplements or recreational drugs. He did not have any food or medications allergies.

Physical examination during the admissions showed the general appearance look moderate ill, the patient was alert and conscious. His vital sign included a blood pressure of 100/60mmHg, a pulse 90 beats per minute (bpm), respiratory rate 20 times per minute, his temperature is 36.7°C and oxygen (O2) saturation was 98% on room air. Both conjunctiva was pale and sclera was not icteric. There was not lymph nodes enlargement at facial, coli, supraclavicular, and axillary. Gingivitis, gum bleeding, and oral plaque were found on mouth examination. Heart, lung, and abdominal examination were not remarkable. Oedema was not found in upper and lower extremity. Extremity examination revealed papular eruption on upper and lower extremity. Other physical examination was not remarkable. Taking into consideration the patient's symptom, sign, history and clinical finding, we were suspected this patient with Anemia and immunocompromised

We performed complete blood count examination that was showed markedly severe anaemia with decreased haemoglobin count of 5.4 g/dL with normal count of MCV 87.6 fL and MCH 26.6 pg, leucocyte count was decreased of 1.610 µ/L, haematocrit was decreased of 23.4%, and platelets count was decreased of 134 /µl, reticulocyte count was decreased of 0.01%, and reticulocyte production index also decreased of 0.1%. We performed anti-HIV rapid test, and the result was reactive, while Hepatitis B surface antigen (HbSAg) test showed non-reactive. $CD4^+$ count showed very decreased of 10 cell/mm^3. Renal and liver function test were normal. Chest X-ray also performed; the result was not remarkable. We assess the patient with Severe Anaemia caused by Anaemia Chronic Diseases (ACD), Stage 4 HIV infection (AIDS) pre highly active antiretroviral therapy (HAART), Wasting Syndrome, Pancytopenia caused by viral infection, Pruritic Papular Eruption, and Oral Candidiasis.

During the admissions, the priority was for severe anaemia. We gave the patient 4 bag packed red cell (PRC) transfusion to treat the anemia. Oral candidiasis was treated by Fluconazole 150 mg once a day and

Cotrimoxazole 960 mg was given once daily to prevent opportunistic infections. After 4 bag PRC transfusion, haemoglobin count was increased 8.8 g/dL, patient's clinical presentation gets a better appearance, no fever, gum bleeding was stopped, and oral candidiasis was decreased. When severe anemia and the opportunistic infections showed good response, the patient was then referred to Prof. I.G.N.G Ngoerah General Hospital to get HAART.

3. Discussion

Advanced HIV Disease is a condition as CD4 cell count <200cells/mm^3 or WHO stage 3 or 4 in adults and adolescents. Anemia is the most common hematological complications in HIV patients especially in AHD. It has a significant impact on quality of life, morbidity, and mortality.[4] People with anemia often suffer decreased quality of life as well as potential increased chance of mortality. A large study of more than 1,200 people with HIV and cancer showed that low hemoglobin levels are associated with greater fatigue and a poor overall quality of life. Incidence of anemia in HIV increases with disease progression, with yearly incidence of 3% in asymptomatic HIV infection, 12% in patients with CD4 counts less than 200 who were otherwise asymptomatic, and 37% in patients with AIDS-related illnesses. Large population studies have showed that the risk of death in HIV with anemia increase independently of the baseline CD4 count, age, or clinical stage of HIV.[7] The patient in this case may defined as AHD because CD4 level is very low of 10 cells/mm^3 and classified as WHO HIV stage 4.[5]

There are three main mechanisms for anemia in HIV infection: decreased red blood cell (RBC) production, increased RBC destruction, and ineffective RBC production. Decreased RBC production may be caused by infiltration of the virus to bone marrow, or myelosuppressive effect, the HIV infection itself, decreased endogenous erythropoietin production, and unresponsiveness to erythropoietin, and hypogonadism.[7,8] Anemia in HIV/AIDS can occurs caused by anaemia of inflammation and also known as anemia on chronic disease. It is characterized by low RBC production as a result of the action of some proinflammatory cytokines such as tumor necrosis factor- α and interleukin-6.[9]

The mechanisms of anemia in this cases could be due to a decrease in RBC production due to suppression in the bone marrow. This can be seen in the patient's complete blood examination which showed reticulocyte count of 0.01 % was below than normal and decreased in reticulocyte proliferation index of 0,1%. A reticulocyte proliferation index (RPI) <2% means anemia indicates decreased production of reticulocytes (i.e. inadequate response to correct the anemia) and therefore RPI >3% means anemia indicates loss of red blood cells (from causes such as hemolysis, bleeding, and etc.) with an increased compensatory production of reticulocytes to replace the lost RBC.[10] Anemia in HIV/AIDS is associated with low reticulocyte counts, demonstrating its hyporegenerative features due to hematopoietic suppression in the bone marrow. This suppression is multifactorial, reflecting the effects of viral infection, inflammation, malnutrition, malignancy and antiretroviral therapy (ART).[2]

HIV infection also can impact bone marrow production and disrupts the bone marrow microenvironment, leading to an increase in inflammatory cytokines, immunoglobulins and acute phase proteins as a response of the host to viral infection. HIV itself may be responsible for impaired haematopoiesis, either through direct infection of Haematopoietic stem/progenitor cells (HSPCs), HIV-induced apoptosis of HSPCs, disruption of the optimal functioning of the stromal cell network within the bone marrow, and HIV associated autoimmune reactions. These mechanisms ultimately lead to the depletion of HSPCs and/or an altered proliferation and differentiation capacity of their progeny.[8] Increased IL-6 induces augmented production of hepcidin, an important regulator of iron homeostasis. The increase of hepcidin is responsible for the retention of iron inside the macrophages and enterocytes, which leads to a decrease in serum iron concentration and hemoglobin production. In addition, IL-1β, TNF-α, and cytokines inhibit the production of erythropoietin, interfering with the proliferation of erythrocyte precursor cells.[2,9]

Increased RBC destruction (hemolysis) or immature destruction of RBC often occurs in HIV infection. Hemolytic anemia can be caused by erythrocyte auto antibodies, hemophagocytic syndrome, Disseminated Intravascular Coagulation (DIC), Thrombotic Thrombocytopenic Purpura (TTP), or glucose-6-phosphate dehydrogenase (G6PD) deficiency.[8]

Ineffective RBC production is another mechanism of anemia in HIV. It can caused by deficiencies in nutrients which are the raw material for forming RBC, so that anemia resulting from this is called nutritional anemia. Nutritional deficiency are common in HIV patients. It can occurs because of secondary infection that may cause oral and esophageal complications such as oral candidiasis and aphthous ulcers, which may reduce food intake and result in hematinic deficiencies such as, iron, folic acid, and Vitamin B_{12} deficiency. Folic acid deficiency is generally caused by deficiencies in both decreased dietary intake and poor absorption. Vitamin B_{12} deficiency can revealed due to malabsorption in distal ileum or from gastric damage caused by opportunistic infections of the gastric mucosa, decreased of intrinsic factor production, and an alteration in the functioning of cobalamin transport protein.[5,7] Iron deficiency in HIV more frequently result of gastrointestinal blood loss from intestinal ulceration, malignancy, or infections.[7] Gastrointestinal bleeding should also be considered in the evaluation of HIV infected patients with anemia. In addition to the usual causes of gastrointestinal blood loss HIV related infections, such as cytomegalovirus colitis and malignancies such as Kaposi's sarcoma and non-Hodgkin's lymphoma that may produce clinically significant bleeding.[5]

Bone marrow infection with Mycobacterium avium complex (MAC) is another common cause of anemia in advanced HIV disease. This infection causes high grade bacteremia and widely disseminated infection, usually involving the bone marrow. In such patients, anemia tends to occur out of proportion to other cytopenias. Infection with B19 parvovirus can also cause anemia in HIV infected patients. B19 parvovirus has been recognized for some time as a cause of severe chronic anemia in immunocompromised persons. Parvovirus DNA has been detected in the serum or bone marrow of some patients with HIV infection and severe anemia. Other conditions associated with HIV infection can cause anemia as a result of direct involvement of the bone marrow such as tuberculosis, histoplasmosis, cryptococcosis, pneumocystis, and non-Hodgkin's lymphoma can all infiltrate the bone marrow generally causing pancytopenia.[5]

Hypogonadism occurs frequently in advanced HIV infection and decreased testosterone has been observed in cross-sectional studies of HIV-related anemia. Testosterone deficiency is therefore likely to be a clinically relevant contributor to anemia in HIV through decreased production of HSPCs.[5,7]

Anemia is diagnosed by a low hemoglobin concentration or a low hematocrit. Anemia can also be diagnosed using RBC count, mean corpuscular volume, blood reticulocyte count, blood film analysis, or hemoglobin electrophoresis.[9] Anemia may be encountered as the initial presentation of an otherwise asymptomatic HIV infection, physicians should be alert to the possibility of HIV infection in every investigation of any case of anemia. All of the HIV patient with anemia need general evaluation to found out the cause of anemia.[7]

A comprehensive baseline history and physical examination may help reduce the number of laboratory tests needed. The physician should also document all previous and current drug use (including prescription drugs, over the counter drugs, and alternative medicine products). Zidovudine (ZDV) is known to be associated with anemia, but the effects of other HIV drugs and drug combinations are not clear and require further study. Morphologically, normocytic normochromic anemia in HIV/AIDS is the most frequent. However, studies also described high frequencies of macrocytosis, usually related to treatment with ZDV. ZDV can interfere with DNA replication and the cell division of erythroblasts, causing macrocytosis in mature erythrocytes. The development of macrocytosis anemia in HIV/AIDS may signify adherence to ZDV antiretroviral regimens.[2,5]

Helpful laboratory procedures include stool testing for occult blood, examining the peripheral blood smear, and taking a reticulocyte count are needed to evaluate anemia in HIV patient. Evaluate of iron stores, test for transferrin saturation, ferritin levels, and total iron binding capacity are needed in HIV patient with anemia. Iron deficiency impairs the response to erythropoietin (EPO) in any patient population, including HIV patients.[11] Deficiencies of vitamin B_{12} or folic acid also impair EPO response that cause many low serum vitamin B_{12} levels in HIV infected patients. Vitamin B_{12} serum level test should performed to detect vitamin B_{12} deficiency[5].

A serum testosterone level should be included in the evaluation of men with anemia and other symptoms suggestive of possible hypogonadism[5,7].

Therefore based on the different characteristics on the causative factors, anaemia is best control by the following steps: Diagnosis and management of the causes of the anaemia, Correcting the haemoglobin value to a therapeutic level, management and prevention of complications.[9]

Management of anemia in HIV patients depends on the underlying cause. The multifactorial causes of anemia in HIV patients are a challenge for physician to treat anemia in HIV. The first step in treating anemia in HIV begins with evaluating the underlying cause. If the cause is known, anemia can be treated according to the cause.[5,9] One of the main management for anemia in HIV is to increases hemoglobin production. Anemia affects the production of RBC as well as the production of hemoglobin due to so many mechanisms. Classical treatment includes erythropoietin (EPO) hormone, erythropoietin stimulating agents (ESAs), iron therapy, and blood transfusions are needed in HIV patient with anemia. Erythropoietin is a glycoprotein hormone, naturally produced by the peritubular cells of the kidney, that stimulates red blood cell production, while ESAs are recombinant versions of EPO produced pharmacologically via recombinant DNA technology in cell cultures. ESAs are generally indicated in conditions where there is impaired RBC production, including in HIV patient.[12] Deficiency of nutrients such as iron and other vitamins results in the decrease of hemoglobin and RBC production.[9] Iron supplements through food enhancement and therapeutics dose improved the iron supplies and increased the synthesis of hemoglobin as well as the RBC production. Iron supplements include oral iron supplements and intravenous iron supplement are also used for the treatment of anemia in HIV.[11]

When anemia occurs in a patient with AHD who has other signs and symptoms suggesting infection or neoplasm, such as fever, fatigue, weight loss, and diarrhea, evaluate the patient for these conditions including treatment and prophylaxis for major opportunistic infections and rapid ART initiation. The successful initiation of ART has lowered the occurrence of HIV-related opportunistic infections that may a good impact to reduced the risk of anemia in AHD patients.[13] Early diagnosis and treatment of HIV infected individuals also can help managed the diseased complications which include anaemia.[9] When anemia has been treated, there is also a need to focus on routine screening and timely management of anemia to prevent disease progression and improve quality of life. In addition, increasing awareness of people living with HIV about the benefits of adhering to a nutritional diet consistently could be useful in managing anemia, as an appropriate diet helps the body in proliferating sufficient red blood cells and other granulocytes in the body.[4]

4. Conclusion

Anemia is the most common hematological complications in HIV patients especially in AHD. It has a significant impact on quality of life, morbidity, and mortality. Anemia can also be diagnosed using RBC count, mean corpuscular volume, blood reticulocyte count, blood film analysis, or hemoglobin electrophoresis. Anemia may be encountered as the initial presentation of asymptomatic HIV infection, physicians should be alert to the possibility of HIV infection in every investigation of any case of anemia. HIV infection may lead to anemia in many ways, there are three main mechanisms for anemia in HIV infection: decreased RBC production, increased RBC destruction, and ineffective RBC production. Evaluate the patient for these conditions including treatment and prophylaxis for major opportunistic infections and rapid ART initiation. Early diagnosis and treatment of HIV infected individuals also can help managed the diseased complications which include anaemia. Management of anemia in HIV patients depends on the underlying cause. The first step in treating anemia in HIV begins with evaluating the underlying cause. If the cause is known, anemia can be treated according to the cause. Classical treatment includes erythropoietin stimulating agents (ESAs), iron therapy, and blood transfusions are needed in HIV patient with anemia.

References

World Health Organization. 2022. Key Facts HIV. Available from https://cdn.who.int/media/docs/default-source/hq-hiv-hepatitis-and-stis-library/key-facts-hiv-2021-26july2022.pdf?sfvrsn=8f4e7c93_5. Accessed 3 October 2023.

Marchionatti, A., Parisi, M.M. 2020. Anemia and thrombocytopenia in people living with HIV/AIDS: a narrative literature review, International Health. 2020;13: 98-109.

Yesuf, T., Muhie, Q.A., Shibru, H. 2019. Prevalence and predictors of anemia among adult HIV infected patients at the University of Gondar Hospital, Northwest Ethiopia, HIV/AIDS – Research and Palliative Care 2019;11: 211-17.

Sah, S.K., Dahal, P., Tamang, G.B., Mandal, D.K., Shah, R., Pun, S.B. 2020. Prevalence and Predictors of Anemia in HIV- Infected Persons in Nepal, HIV/AIDS – Research and Palliative Care 2020;12: 193-200.

Iddah., Ali, M. 2019. Anaemia in HIV, EAS Journal of Parasitology and Infectious Diseases 2019;1(4): 73-84.

Demitto, O.F., Pereira, M.A., Schmaitz, C.A., Anna, F.M.S., Arriaga, M.B., Andrade, B.B., et al. 2020. Impact of Persistent Anemia on Systemic Inflammation and Tuberculosis Outcomes in Persons Living With HIV, Frontiers in Immunology 2020;11: 1-13.

Seddon, O., Freedman, A., Scadden, D.T. 2017. Secondary Anemias: HIV and Anemia. In: Anemia Pathophysiology, Diagnosis, and Management. Cambridge University Press, United Kingdom, p. 167-171.

Durandt, C., Potgieter, J.C., Khoosal, R., Nel, J.G., Herd, C.L., Mellet, J., et al. 2019. HIV and haematopoiesis, South African Medical Journal 2019;109(8): 541-46.

Bashiru, A.G., Yakubu, A., Kwaifa, I.K., Alhassan, H.M., Shittu, S.B., Abubakar, U., et al. 2023. Anaemia in subsaharan Africa: A review of causes, risk factors, diagnostic challenges and evident based management, International Journal of Scholarly Research and Reviews 2023;02(02): 035-044.

Gaur, M., Sehgal, T. 2021. Reticulocyte count: a simple test but tricky interpretation, Pan African Medical Journal 2021;40(3): 1-3.

Peng, L., He, Y., Zhang, J., Hong, D., Li, G. 2022. Erythropoietin and iron for anemia in HIV-infected patients undergoing maintenance hemodialysis in China: a cross-sectional study, BMC Nephrology 2022;23(60): 1-6.

National Library of Medicine, 2023. Erythropoietin Stimulating Agents. Available from http://www.ncbi.nlm.nih.gov/books/NBK536997/. Accessed 20 October 2023.

National Library of Medicine, 2023. HIV-1–Associated Opportunistic Infections. Available from https://www.ncbi.nlm.nih.gov/books/NBK539787/. Accessed 7 October 2023.