Nigerian Medical Journal
NIGERIA MEDICAL ASSOCIATION
Print ISSN 0300-1652, E-ISSN 2229-774X

Case Report

Haemolytic anemia in a patient of Chronic myeloid leukemia: an unrecognized side-effect of Hydroxyurea?

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Abstract

Hydroxyurea (HU) is frequently used in the treatment of various myeloproliferative neoplasms (MPN) where it reduces cell proliferation by impairing DNA synthesis leading to decreased hematopoiesis. Herein we report a case of a 65-year-old female who was diagnosed with Chronic myeloid leukemia and developed severe hemolytic anemia requiring multiple packed red blood cell (RBC) transfusions while being treated with hydroxyurea. The haemolysis persisted until discontinuation of the drug. Common side-effects of HU like macrocytic anemia, leucopenia, and thrombocytopenia are well known but hemolytic anemia is a rare side-effect, not well known with only a handful of cases being described in the scientific literature so far.

Keywords: *Hydroxyurea; Hemolytic Anemia; Myeloproliferative Neoplasm; Side Effect.*

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How to cite: Jamal I, Smita S, Choudhary V. Hemolytic anemia in a patient of Chronic myeloid leukemia: an unrecognized side-effect of Hydroxyurea? Niger Med J 2024;65(6):1171-1175.https://doi.org/10.60787/nmj.v65i6.576.

Quick Response Code:

Introduction:

Hydroxyurea is frequently used in the treatment of various myeloproliferative neoplasms (MPN). The main effect of hydroxyurea is to reduce the cell count by impairing DNA synthesis thereby leading to a decreased haematopoiesis. It is also used in the treatment of sickle cell anaemia, bringing about increased levels of foetal haemoglobin and reducing the number and severity of crises. Hydroxyurea has been available since the 1960s and much knowledge has been gained from the use of hydroxyurea as a cytoreductive agent and from the side effects that accompany its use. The main side effects include macrocytic anaemia, leukocytopenia, and thrombocytopenia. In this report, we describe haemolytic anaemia resulting from the use of hydroxyurea. This is a rare side effect and only a few cases have been described in the literature so far.

Case report:

A 65-year-old female presented with low-grade fever, weakness, and abdominal heaviness for the past 6 months. On clinical examination, she had pallor and massive splenomegaly. Complete blood count revealed hemoglobin of 8.9 gm/dl a total white blood cell (WBC) count of 3.5 x 10^9L with the presence of 2% blasts and 6% basophils and left shift with myelocyte bulge. The platelet count was adequate (1.5 x10^9/L) and the blood film showed microcytic hypochromic red blood cells (RBCs), tear drop cells, and few nucleated red cells were noted on peripheral blood smear.

Bone marrow aspirate was hypercellular with marked myeloid proliferation and myelocyte bulge. Blasts and basophils accounted for 4% and 9% of all nucleated cells of bone marrow respectively. The megakaryocytes were mildly increased with few dwarf forms and loose focal clustering noted at places. With these clinical and hematological findings, a diagnosis of chronic myeloid leukemia-chronic phase (CML-CP) was made. BCR-ABL fusion study was advised but due to financial constraints patient deferred this test to a later date. Meanwhile, to reduce the burden of hyperleukocytosis hydroxyurea was started in a dose of 500 mg three times daily (TDS). Her total WBC count was reduced to 15000/mm^3 after 3 months. However, she suddenly developed shortness of breath and fatigue after a month of starting hydroxyurea. Her repeat CBC revealed hemoglobin of 6.3g/dL, WBC count of 15000/mm^3, and platelet count of 1l/mm^3.

Peripheral blood smears showed marked anisopoikilocytosis, microcytic hypochromic RBCs, polychromatophils, and 100nRBCs/100 WBC. Basophils were occasionally seen; however, blasts were absent. A follow-up bone marrow aspirate showed erythroid hyperplasia with many erythroid clusters displaying predominantly normoblastic maturation. (Figure 1A-1C)

Serum Lactate dehydrogenase (LDH) was 839IU/L (normal range 100-280 IU/L), Haptoglobin was 20mg/dl, reticulocyte count was 15% and total bilirubin was 4.5mg/dL(direct:1.2mg/dL and indirect: 3.3mg/dL). Direct and indirect Coombs tests were negative. Cold agglutinins were not found, vitamin B12 and folate acid levels were normal and there were no schistocytes in the blood smear.

Repeated laboratory examinations revealed persistent hemolytic anaemia. Due to the absence of other causes of hemolysis, the possibility of hemolytic anaemia due to the use of hydroxyurea was considered.

Treatment with hydroxyurea was stopped and replaced by Imatinib. Hereafter, the haemoglobin rose from 6.3 gm/dL to 8.4 gm/dL, and serum haptoglobin, bilirubin, and LDH levels also returned to their normal values. A repeat peripheral blood smear showed a complete absence of nucleated red cells.

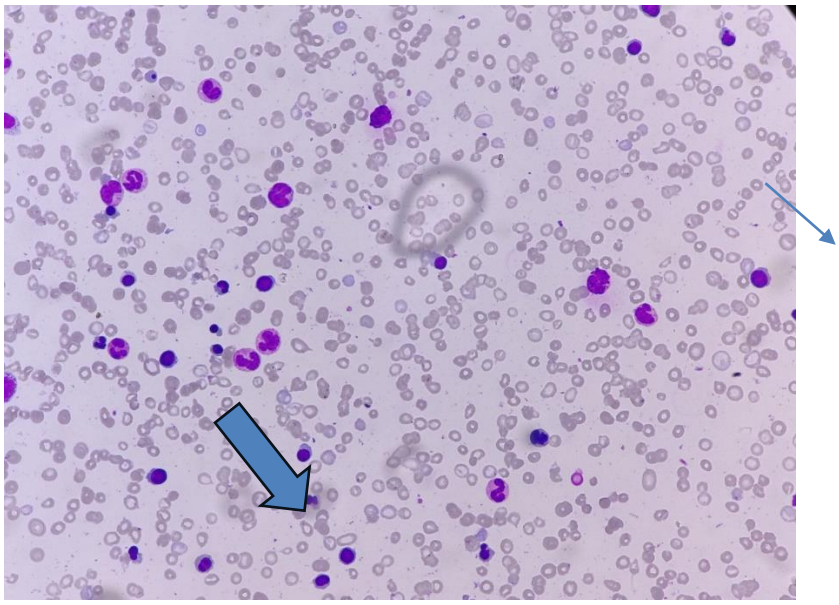

Figure 1A: Microphotograph of peripheral blood smear showing the presence of plenty of nucleated RBCs (shown by broad blue arrow) with microcytic hypochromic RBCs and few micro spherocytes (thin blue arrow), polychromatophils and target cells. (Leishman stain; 400X)

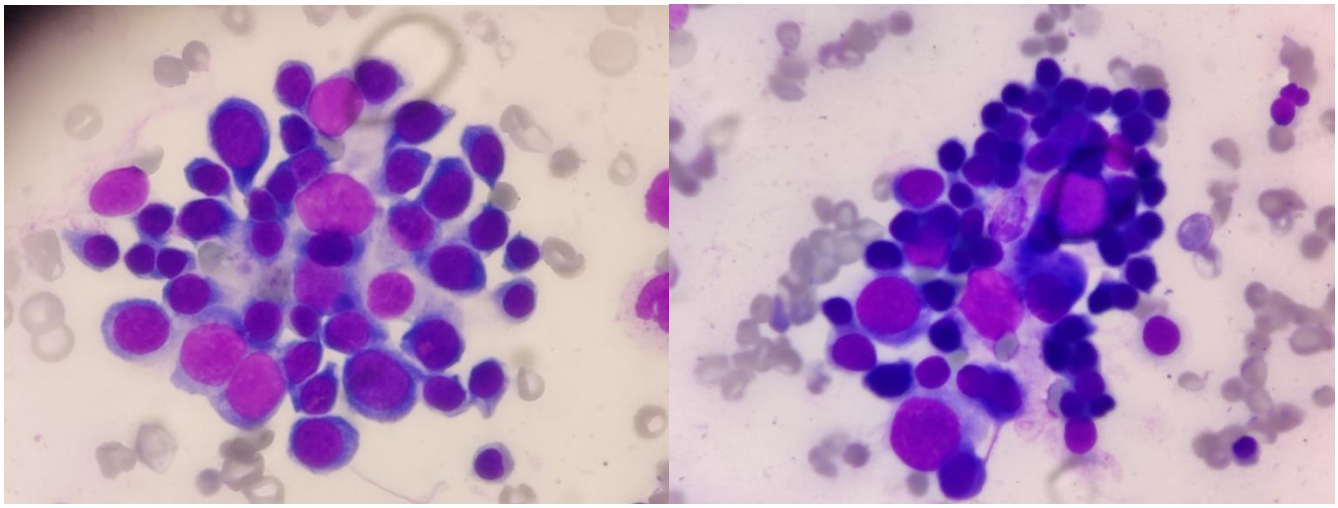

Figure 1B & 1C: Microphotograph of bone marrow aspirate showing erythroid hyperplasia with tight erythroid clusters with normoblastic maturation. (Leishman Stain; oil immersion lens)

Discussion

Hemolytic anaemia is a rare side effect of hydroxyurea. To our knowledge, only a few cases report hemolytic anaemia due to the use of hydroxyurea [2,3,5,10] as shown in Table 1 with a clear description by Jabr et al 2004[3]. The first case involved an 80-year-old male with Essential thrombocythemia (ET) who was treated with hydroxyurea. The patient developed hemolytic anaemia after two and a half years of treatment with a negative DAT. [2] No other explanation for the haemolysis was found and it ceased when the hydroxyurea was discontinued. The second case describes a 61-year-old male treated for ET, in which hemolytic anaemia developed after five years of treatment with hydroxyurea.[3] There was also a series of nine patients (Kennedy et al. 1966) [5] with chronic myeloid leukaemia who were treated with hydroxyurea at a dose of 50 mg/kg/day, in which two patients developed hemolysis after six months of treatment. However, no further analysis of the hemolysis is described.[5] The cases described above prove that the use of hydroxyurea not only leads to anaemia by impaired haematopoiesis, but that hemolysis is

also possible. It scores a 9 on the Naranjo scale for the probability of adverse drug reaction, indicating a proven side effect.[6] The mechanism that leads to this hemolytic anaemia is unclear. One possible mechanism might be the denaturation of haemoglobin caused by oxidative stress, resulting in hemolysis. This has been described before in an in vitro study (Roa et al., 1997).[7] Another mechanism might be that due to impaired DNA synthesis, ineffective erythropoiesis causes hemolytic anaemia, such as seen in patients with severe vitamin B12 deficiency.[8] Activation of the complement system can also lead to hemolysis. However, DAT should be positive in such cases. It might be that hemolytic anaemia due to the use of hydroxyurea is a more common side effect, but it is not recognised. This might be because macrocytic anaemia is a side effect that is frequently seen and is attributed to the suppression of hematopoiesis.[9]

Hydroxyurea is frequently used in the treatment of chronic myeloproliferative neoplasms. Hydroxyurea-induced hemolytic anemia is a very rare side-effect of this drug. Both the hematopathologists and clinical hematologists should be aware of this adverse reaction to reach a correct diagnosis and further management. There are a few unanswered questions as to why hydroxyurea leads to hemolysis in only a few patients; why this side effect is not seen in the most patients with hydroxyurea and why the duration of development of hemolysis varies in different cases as shown in Table 1. In addition, there is still a lack of clarity on what is the exact mechanism of development of this side effect. These questions still require valid explanations, hence more such studies are required to establish the exact etiopathogenesis of this side-effect of Hydroxyurea.

Table 1: Showing previous case reports of hydroxyurea induced hemolytic anaemia and case characteristics

Name of the Author with year	**Age /sex**	**Chronic myeloproliferative neoplasm diagnosed**	**Duration of development of hemolysis after treatment with Hydroxyurea**
Kennedy et al,1966[5]		CML (09 cases)	Two of them developed hemolysis after 6 months
Jabr et al, 2004[3]	80/Male	ET	2.5 years
Lugito et al,2018[2]	61/Male	ET	5 years
Cornelisse et al,2020[10]	59/Male	ET	6 years
Present case	65/Female	CML	3 months

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