POSSIBILITY OF LEUKOGENICITY EFFECT OF LONG TERM USE OF HYDROXYUREA IN SICKLE CELL ANAEMIA
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ABSTRACT: Malignancy in patient with Sickle Cell Anemia has been reported by many researchers, but the type of malignancy and its incidence remain undefined. Before this case report; the association of chronic myeloid leukemia in sickle cell patients, 5 cases were reported in 2005, 9 cases reported in 2008 and then 10 cases in the year of 2011. Hydroxyurea is an antimetabolite that minimizes pain and prolongs survival in patient with Sickle Cell Anemia. This drug is more widely prescribe in sickle Cell anemia patients in Chhattisgarh State where such disease have high prevalent. Leukemogenic risk of Hydroxyurea is extrapolated from its reported risk in myeloproliferative disorders. Long term studies on effect of Hydroxyurea in Sickle Cell Disease children have been reported by many researchers. In this case leukemia may be related with long term use of Hydroxyurea but for accurate interpretation of future reports of malignancy in patient with Sickle Cell Disease, especially those receiving Hydroxyurea must be monitored.

KEYWORDS: SCA, CML, HU.

INTRODUCTION: Hydroxyurea is an antimetabolite that minimizes pain and prolongs survival in patients with sickle cell anemia.¹ Sickle cell disease (SCD) is one of the most common genetic diseases in Chhattisgarh, India. Most patients suffer intermittent pain crises and life-threatening events while life expectancy is considerably reduced. Until the last decade management was purely preventative or supportive aimed at symptom control. Apart from stem cell transplant, there is no cure but the oral chemotherapeutic drug Hydroxyurea (HU) has now established a role in ameliorating the disease and improving life expectancy for most patients. There are side effects and risks of HU treatment in SCD but for moderate and severely affected patients, the benefits can be significant. It is very widely prescribe by the physician treating the sickle cell anemia just to reduce the episode of sickle cell crisis by increasing the fetal hemoglobin.² Leukemogenic risk of Hydroxyurea is extrapolated from its reported risk in myeloproliferative disorders.³ Hematologic Malignancies in patient with sickle cell anemia are rare. Very few cases have been reported worldwide. The awareness and possibility of sickle cell anemia and coexisting malignancies have undergone tremendous changes. Reported malignancies with sickle cell anemia patients are acute lymphoblastic leukemia, chronic granulocytic leukemia, multiple myeloma malignant histiocytosis, non-Hodgkin’s lymphoma, Cutaneous T cell lymphoma and chronic lymphocytic.⁴ This is the first case report on sickle cell anemia with chronic granulocytic leukemia which comes to our knowledge in the region of Chhattisgarh.

CASE HISTORY: A 30 years old female a known case of Sickle cell anemia was admitted in medical ward, complaining of huge lump in abdomen with 6 month history of low grade fever, fatigue, night sweats. She had remarkable pain in abdomen & left hypochrondium for 4 month. She had past history
of vaso-occlusive crisis. She received approximately 10 unit of whole blood transfusion during last 2 year. She was under medication of Hydroxyurea for more than 15 years the treatment of her disease. Her physical examination revealed huge spleenomegaly mild hepatomegaly, bilateral axillary lymphadenopathy, Pallor and mild jaundice. Complete blood count through five part Hematology Analyzer Pentra-60 (Horiba-ABX, Span) showed Hemoglobin 7.8Gm/dl and high leukocyte count 82,000/cu mm, Hematcrit 28.8%, MCV 88/f l, MCH 23.7 pg, MCHC 26.9g/dl, platelets 373000/µL.

When the patient’s leukocyte count was elevated and was found positive for sickle cell test by Sodium Meta bisulphate oxygen reduction test, then the patient was examined and investigated in detail. Spleen was enlarged up to pelvis and liver was enlarged up to costal margin in Sonography. Liver enzymes were elevated. High Performance Liquid Chromatography (HPLC) conducted through D-10 (Biored, USA) for hemoglobin shows Sickle Hemoglobin 30.4%, Fetal hemoglobin <0.8 % Hb A1 C 4.8% and Hb A2 4.2%, Peripheral Blood picture showed marked red cell anisopoikilocytosis, drepanocytes, with fare number of Narmoblasts (7NRBC/100 RBC).

White Blood cell series presented with fair number of Metamyelocytes 17% Promyelocytes 07% and Band cells 14%, Myeloblasts 04%, Myelocytes 11%, Basophils 12% Monocytes 20%, Lymphocytes 09% and mature Neutrophils 06 %. Bone Marrow aspiration & examination revealed depressed erythropoiesis, leukocytes hyperplasia with shift to left predominantly Promyelocytes, Metamyelocytes and Myeloblasts promotion diagnosis of chronic Myeloid leukaemia.Cytological evaluation of peripheral blood sample confirmed a Karyotype of 46 XX T (9,22) (q 34;q 11.2); confirming the diagnosis of chronic Myelogenous leukemia.

**DISCUSSION:** The development of malignancy in persons with Sickle cell anemia has been documented by various researches.(5-15) Hodgkin’s lymphoma as first hematologic malignancy reported neoplasm in sickle cell disease in 1938.(5) Frequency of different hematologic malignancy since 1960 in sickle cell disease patients reported in 1998.(16) Hydroxyurea has been used for since so long for management of Sickle cell Anemia to reduce the number of painful episodes.(17) Long term safety of the drug, in particular of its Leukemogenic potential is still questionable. Leukemia has been reported in myeloblastic syndrome after at least 3-4 years of exposure of to the drug.(17-18) Long term studies on effect of Hydroxyurea in Sickle Cell Disease children has been reported by many researchers.(19-20)

Before this case report, highlighting the association of chronic myeloid leukemia in sickle cell patients, 5 cases were reported in 2005(21) 9 cases reported in 2008 and then 10 cases in the year of 2011,(22) 2 cases were found in combination of Sickle/βO Thallassamia with Chronic myeloid leukemia.(4)

The possible explanation for the rarity of hematologic malignancy such as Chronic Myeloid Leukemia, present in sickle cell anemia is the short life expectancy of these patients. With modern medical care, the average life expectancy of sickle cell disease patients has improved in both the genders, therefore more hematologic malignancy along with other complications are expected to be observed in elderly patients with sickle cell anemia(21) In present reported case Chronic Myeloid Leukemia with Sickle Cell Disease is at the age of 30 years. Ferster et al refer to a malignancy in one SCD on Hydroxyurea.(23) A case of leukemia with background of cells suggesting myelodysplasia was reported in a 27 years old SCD patient on Hydroxyurea treatment for 8 years.(24)

Many sickle cell disease patients have been managed effectively with Hydroxyurea for several years with no report termination into neoplastic condition. In present case report patient had
received Hydroxyurea for the period of 15 years & had received multiple blood transfusions the duration of 2 years.

Hydroxyurea reduce d NTP pools, thereby interfering with both DNA synthesis and repair mechanism.\(^{(22)}\) In vivo, hydroxyl urea prevents complete repair of DNA damage, leading to accumulation of somatic mutation and chromosomal damage. In vivo Hydroxyurea therapy has been suggested to increase the risk of acute leukemia for the patient with Myeloproliferative disorder\(^{(18,25)}\) but its carcinogenic potential in other clinical settings is much less compelling and no adults up to 9 years of drug exposure have had secondary leukemia develop\(^{(26)}\). Moreover, quantative analysis of acquired DNA mutations suggest that mutagenic potential hydroxyl urea for patient with Sickle Cell Disease is low\(^{(27)}\) however, anecdotes of Malignancy or Myelodysplasias in patient with Sickle Cell Disease on Hydroxyurea are emerging\(^{(24,28)}\) consideration of its carcinogenic potential should be given, because more and more sickle cell anemia may be treated with Hydroxyurea and pathology should be altered to this potential.

Special risk factors related to malignancy formation in Sickle Cell Disease have been proposed which include infection (e.g. human immunodeficiency virus or hepatitis C), transfusion-related immune-modulation, and persistent cellular and organ damage induced by stimulation of inflammatory cells due to Vaso-Occlusive phenomenon leading to granulocytic cell differentiation and Chronic Myeloid Leukemia and exposure to bone marrow transplantation or modern chemotherapy such as Hydroxyurea\(^{(4,29)}\).

The leukocytosis with depressed erythropoiesis picture, in peripheral blood as considered as secondary reaction to sever anemia, infection or other stresses that commonly occur in patient with sickle cell anemia. As demonstrated in this case Chronic myeloid leukemia should be included in differential diagnosis in patient with sickle cell anemia with hepato-spleenomegaly and also advent of Hydroxyurea therapy, immune-modulation, viral infection, stem cell transplantation through multiple blood transfusion to be put in consideration for emerging cases of Chronic myeloid leukemia in Sickle Cell Disease. In this case leukemia may be related with long term use of Hydroxyurea. Data presented with different researchers are very less but possibility of malignant potential of Hydroxyurea cannot be ignored. For accurate interpretation of future reports of malignancy in patient with Sickle Cell Disease, especially those receiving Hydroxyurea must be monitored.

REFERENCES:
