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Virology

LAMIVUDINE INDUCED PURE RED CELL APLASIA IN KNOWN CASE OF HIV :A RARE CASE REPORT

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ABSTRACT We are presenting a case of a middle aged male who was a known case of retroviral disease presented with pure red cell aplasia due to lamivudine treatment. The patient was admitted in view of breathlessness on exertion and generalised weakness and fatiguability. On admission, routine blood tests revealed a hemoglobin of 2.3 g/dL with normal leukocyte and platelet counts, indicating single lineage involvement . His blood tests were negative for any autoimmune causes, infective causes like parvo virus and his anaemia persisted even after stopping zidovudine. After stopping lamivudine treatment, the patient's hemoglobin concentration and hematocrit level returned to normal. In above mentioned case Lamivudine was found to be a cause of pure red cell aplasia.

KEYWORDS : Anemia , Lamivudine, Pure red cell aplasia

INTRODUCTION:

Anemia is a most common haematological abnormality seen in patients of HIV infection. It is thought to occur due to virus activity itself affecting bone marrow. Patients of end stage retroviral disease are most common to get affected. Anemia can remain asymptomatic or can present as dyspnea on exertion, Fatiguability, reduce exercise tolerance depending upon severity of anemia.[1]

There are various causes of anemia in patients of retroviral disease which includes direct involvement of bone marrow by virus, deficiency of erythropoietin, opportunistic infections like mycobacterial or fungal infections. Non Hodgkin lymphoma which is a one of the most common associated disorder with HIV can present with severe anemia. Also Nutritional deficiencies of Iron, folic acid, Vitamin B12 can cause anemia. Iatrogenic causes involving use of HAART including zidovudine, lamivudine, Zalcitabine can lead to anemia.[2]

Anemia is one of the common finding seen in patients of Retroviral disease who are on treatment with Nucleoside Reverse Transcriptase Inhibitors (NRTI's) which includes Zidovudine, Zalcitabine. Zidovudine being cost effective and efficacious drug in treatment of HIV is commonly being used. Anemia Is one of the most common side effect of zidovudine hence frequent monitoring of blood counts is mandatory in patients using Zidovudine.[3][4] ZDV inhibits the proliferation of Hematopoietic progenitor cells in a dose-dependent manner and can lead to anemia[5][6]

Occurrence of pure red cell aplasia in patients of retroviral disease is rare. There are many cases reported of Patients suffering for red cell aplasia in patients of HIV secondary to parvo virus infection and Zidovudine[8][9] .Lamivudine induced pure red cell aplasia is a rare occurrence and is rarely seen entity. There are very few cases of Pure red cell aplasia in patients of HIV on lamivudine therapy reported so far. [10][11]Lamivudine induced pure red cell aplasia can cause anemia which can remain unresponsive to treatment in patients of HIV. There are possibilities of synergistic action of Lamivudine and Zidovudine leading to pure red cell aplasia and myelodysplasia. Studies have shown that lamivudine and Zidovudine can inhibit colony formation of human hematopoietic progenitor cells. [7]

Case report

We present a case of pure red cell aplasia in patient suffering from retroviral disease who was on treatment of lamivudine A 45yr old male complaining of breathlessness on exertion and generalised weakness since 3 months was admitted for evaluation and treatment. Patient was a known case of Retroviral disease on regular treatment since 10Yrs. Patient was on HAART including Zidovudine, lamivudine, efavirenz therapy. Because of persistent anemia zidovudine was stopped and patient was started with Tenofovir Lamivudine and Dolutegravir. There was no history suggestive of blood loss, bleeding tendencies. There was no history of any chronic illness including tuberculosis in past. Patient gave significant history of frequent blood transfusion since 10 months, with frequency of 2 – 3 transfusions per month.

On general examination patient appeared conscious, oriented and cooperative. His Pulse rate was 86 bpm and Blood pressure was 110/70 mm Hg with oxygen saturation of 97% on room air. Patient had severe pallor evident over palpebral conjunctiva ,mucous membranes and palmar creases. There was no icterus, clubbing, cyanosis or lymphadenopathy seen. There were no signs of any opportunistic infection, including Tuberculosis and there were no signs of GI bleeding and other malignancies.

Systemic examination appeared to be normal for cardiovascular system, respiratory system and central nervous system. On per abdominal examination there was no organomegaly and no tenderness.

On Further evaluation, serial blood count was as follows :-

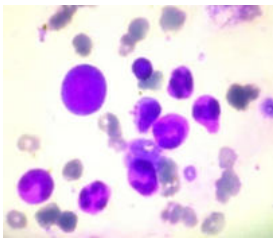
Parameters	22-04-2021	12-05-2021	15-05-2021(after blood transfusion)	10-06-2021	12-06-2021 (after blood transfusion)
Hb	4.1	2.3	7.2	1.6	4.5
MCV	97.69	79.5	87.5	75	74.5
RBC	1.3	0.88	2.48	0.80	1.88
Platelets	125000	181000	133000	11000	142000
TLC	4900	4700	11870	6400	5900

Other blood investigations revealed CD4 count of 320 cells/cu.mm. Direct and indirect agglutination test were negative, reticulocyte count – 0.30 %, Reticulocyte production index (RPI)-0.1 Immature reticulocyte fraction (IMF) 1.20 % (2-16.50), Reticulocyte hemoglobin of 24.8 pg (28.7-34.1) Immature platelet fraction(IPF) of 9.2 % (1-6). His Creatinine level was 1.32 mg/dl Urea -42 mg/dl, Total bilirubin-0.8 mg/dl, Direct bilirubin-0.4 mg/dl, Indirect bilirubin-0.4 mg/dl. His serum SGOT was 61.8 U/L, Serum SGPT-109.0 U/L, Total proteins-7.7 g/dl, Serum albumin-4.4 g/dl, Serum Globulin -3.3 g/dl, INR of 1.10, LDH-694 U/L, Serum ferritin- 1000 ng/ml (10-291), Serum iron- 357µg/dL (33-193), Serum UIBC- <17µg/dL (125-345), Serum TIBC- 374µg/dL (250-450), Transferrin saturation-95% (14-50), Serum Vitamin B12 level-1169 pg/mL (187-883). Stool examination was negative for occult blood.

Peripheral smear was suggestive of normocytic, normochromic anemia. Bone marrow studies showed Hypercellular marrow with adequate megakaryocytes, with markedly reduced erythroid cells. Differential count was Blasts – 2%, Promyelocytes-13%, Myelocytes-24%, Metamyelocytes-17%, Neutrophils-36%, Lymphocytes-5%, Monocytes-2%, Eosinophils-1%, Iron stain - Iron stores 4+ Mildly increased .No ring sideroblasts were seen. Above findings showed very occasional erythroid precursors. However, mature erythroid forms were absent suggestive of **Hypercellular bone marrow with marked erythroid suppression ,consistent with Pure Red Cell Aplasia.**

Patients PCR test for Parvovirus B19 was negative. Which ruled out parvo virus B19 infection which is one of the most common cause for pure red cell aplasia.

Above investigations was able to diagnose pure red cell aplasia but was unable to find cause of pure red cell aplasia. Patients HAART regimen was changed from Tenofovir, Lamivudine and Dolutegravir to Lopinavir, Dolutegravir and ritonavir. Patient was the followed for few months and serial CBC revealed rising hemoglobin with improving hematocrit levels.



Bone marrow of patient

DISCUSSION:

Anemia is a frequent finding associated with the human immunodeficiency virus type 1 (HIV-1). The most common cause of anemia is the disease itself followed by ART drugs . Among the ART drugs Zidovudine is the most common culprit . Lamivudine is the rare cause of anemia which can lead to pure red cell aplasia . Hence in a patient of HIV who comes with anemia, through investigation should be carried out and cause of anemia should be detected . With proper treatment the anemia could be corrected and quality of life can be improved.

``Multifactorial origin of anemia makes it difficult find the original cause and/or its proper treatment. It complicates the disease progression , decreases the quality of life and increases the risk of death. Hence it is very crucial to find the cause of anemia and treat the patient accordingly which helps to improve the quality of life of HIV patients.

The HIV patients can have anaemia due to disease itself , HIV proteins and cytokines have been suggested to inhibit growth of hematopietic cells in the bone marrow of HIV-infected patients.[12]
Opportunistic infections like TB , can cause for anaemia in a large number of HIV-infected patients which can be easily treated by treating the underlying infection.[12]

Iatrogenic ie. Drug induced anemia is the most commonly cause seen in HIV patients . Zidovudine is most commonly used as therapy because of easy affordability and low cost. There are many studies that the zidovudine can cause anemia .[13] Zidovudine causes red cell hypoplasia or aplasia. Bone marrow examination demonstrate pure red cell aplasia, erythroid maturation arrest, erythroid hypoplasia and megaloblastic erythropoiesis. ZDV inhibit hemoglobin synthesis and globin gene transcription . ZDV specifically inhibits beta-globin gene expression in human erythroid progenitors leading to marked cell growth inhibition at clinically relevant concentrations [14]

Lamivudine is a very rare cause of anemia in HIV positive patients. Lamivudine can cause pure red cell aplasia . There are some studies of lamivudine induced PRCA.[10]Lamivudine Is the first line regimen used in HIV patients . Mechanism of anaemia is similar to zidovudine ie.inhibition of colony formation of human haematopoietic progenitors.

Pure red cell aplasia(PRCA) is a rare bone marrow disorder characterized by absence of erythropoiesis and severe nonregenerative anemia. Congenital form is known as Diamond blackfan syndrome. Secondary causes of PRCA are certain medications, infections, pregnancy, renal failure, and conditions such as thymomas, autoimmune disease (such as systemic lupus erythematosus), cancers of the blood, and solid tumors.[15][16] Drugs causing PRCA are phenytoin, azathioprine, isoniazid ,sodium valproate , allopurinol , tacrolimus and lamivudine.

CONCLUSION:

Anemia is the most common finding seen in HIV patients . The etiology of anemia should be detected by thorough workup . Most causes of anemia are treatable if detected at the early stage .Most of the ART drugs used can cause anemia. Stopping the culprit drug and changing the regimen leads to improvement in anemia. Hence early detection and treatment lead to improved survival of the HIV patients and prolongs the survival.

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