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CASE REPORT

Hydroxyurea induced Liver Injury with significant eosinophilia in a case of sickle cell anaemia

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Abbreviations

HU: hydroxyurea, LFT: Liver function tests, HRCT: High resolution computed tomography, DILI: Drug induced Liver Injury, RUCAM: Roussel Uclaf Causality Assessment Method, SCD: Sickle cell diseases.

Keywords: Hydroxyurea, Drug induced Liver Injury, RUCAM, Sickle cell diseases, Sickle Hepatopathy, Eosinophilia

Objective

Rare case report of Hydroxyurea induced Liver Injury with significant eosinophilia in a case of sickle cell anaemia.

Methods

Mr. DE, a 28-year-old male, resident of Nigeria, known case of sickle cell diseases, since childhood, requiring frequent blood transfusion and having low grade indirect hyperbilirubinemia. He came to India for further treatment, started on hydroxyurea, but three weeks after starting HU, he developed acute abdominal pain, nausea and vomiting along with yellow discoloration of eyes. For these complaints he was consulted in Hepatology OPD and suspected to have acute viral hepatitis, drug induced liver injury and other sickle cell related liver dysfunctions (sickle hepatopathy, obstructive jaundice). Hydroxyurea (HU) was withheld. Liver function tests (LFT) showed direct hyperbilirubinemia with raised liver enzymes (T. bilirubin =35.13mg/dL, Direct = 31.09mg/dL), complete blood count (CBC) showed eosinophilia, viral work up was sent (CMV DNA, EBVIgM, HBsAg, Anti-HCV, HIV I and II, Anti HAVIgM, Anti HEVIgM), all were negative. After stopping the HU, his jaundice improves with intravenous fluid, fat free diet and other supportive

care, as shown in Table 1. His UGIE showed hiatus hernia and esophagitis. Antinuclear antibody (ANA) and IgG were normal. Absolute eosinophil count (AEC) was 4600 cells/microliter of blood, in repeated investigations eosinophils went up to 38%, as shown in Table 1, therefore , through evaluation was done to rule out Hyper eosinophilic syndrome(HES) including , serum IgE levels -6105 IU/ml(normal <100 IU/ml) , echocardiography , pulmonary function test (PFT), electrocardiogram (ECG), stool test and ,HRCT chest all were within normal limits . Empirical deworming done with albendazole in view of eosinophilia and no identifiable cause, and it was presumed to be DILI related. Alternate causes and risk factors were ruled out for liver dysfunction and DILI. Latency period was 21 days. Other Concomitant drugs or potential hepatotoxins were not present. Lab tests revealed elevations in liver enzyme function tests, which resolved promptly after cessation of HU, but eosinophilia was persisting, therefore he was started on steroids and after that eosinophilia improved. After recovery of this episode, in view of his severe sickle cell diseases, he was re-challenged with HU, which again showed worsening of the liver functions in 10 days, which again recovered with stopping the drug. RUCAM score for DILI was 9, all alternative diagnosis for liver injury and eosinophilia were ruled out. Hydroxyurea related DILI with eosinophilia a rare entity and seldom reported.

Results and Discussion

Sickle cell disease (SCD) is an inherited disorder of red blood cell, where shape of RBC is deformed to a shape like sickles, which predispose them for hemolysis. The most frequently occurring form of SCD is sickle cell anemia (HbSS), followed by sickle-hemoglobulin C (HbSC) and sickle-beta (HbS/beta)-thalassemia. Low grade hemolysis continues, and mild indirect hyperbilirubinemia is a common phenomenon. In stressful conditions like sepsis, dehydration, or acidosis etc. patient can develop acute crisis with life threatening manifestations involving different organs, and patient can develop worsening jaundice.

Liver dysfunctions are rarely reported adverse event with the use of HU and eosinophilia is also very rare event. The manifestations range from benign hyperbilirubinemia to overt liver failure, with the spectrum of acute clinical presentations often referred to as “sickle cell hepatopathy”.[1,2] This is an umbrella term referring to liver dysfunction and hyperbilirubinemia due to intrahepatic sickling process during SCD crisis leading to ischemia, sequestration and cholestasis. Exchange transfusion may be the only effective management for initial episodes of severe sickle cell hepatopathy.

Due to sickling process, patient can develop vascular complications from the sickling process, multiple transfusions requirement increases the risk for viral hepatitis, iron overload, and (combined with the effects of chronic hemolysis) the development of pigment gallstones, all of which may contribute to the development of liver disease. Sickle cell hepatopathy occurs predominantly in patients with homozygous sickle cell anemia, and to a lesser extent in patients with HbSC disease or HbS/beta-thalassemia.[3,4] The overall incidence of liver disease in patients with sickle cell disease (SCD) has not been well established. Table 2 showed possible causes of jaundice in SCD.

Treatment of sickle cell diseases and crisis involves supportive care and HU, which is an oral medicine and requires daily administration, which can reduces the frequency of painful crises, the need for blood transfusions and hospitalizations. This is a very commonly used medicine, in hematology practice, but can have some adverse effects, like nausea, vomiting, diarrhoea., loss of appetite, constipation , oral ulcers or skin rash.

In our case, patient has severe acute hepatitis, drug related, manifested as prodromal symptoms, and clinical signs of acute liver injury. Patient was having jaundice, rise of enzymes and peripheral eosinophilia, which all recovered, with cessation of drug and on re challenge there was re-appearance of the signs and symptoms and resolved with discontinuation again. This form of liver injury in contest of SCD and HU, is rarely reported, above manifestations, does not come in paradigm of Sickle cell hepatopathy. HU related DILI can have varied manifestations, from mild to severe liver injury.[5] DILI in general is managed by cessation / removal of the culprit agent, but in extreme case, need of liver transplant may be required.[6] Therefore, treating physicians, especially oncologist and hepatologist, should be aware of this rare adverse event of this drug.

Eosinophilia can be present in sickle cell anemia itself as demonstrated in a study by Canalli AA et al,[7] where they postulated that increased number of eosinophils can results in acute crisis and, in the vasoclusive process. In a study in abstract form by Pallis et al[8] showed that eosinophil (Eos) of patients with SCA demonstrates a higher capacity for spontaneous migration, stimulated migration, and degranulation. Therapy with HU is associated with reduced adhesion and degranulation of EOs in these patients but had no effect on the chemotactic ability of these cells or chemokine levels. The characteristics of the effect of HU on EO also suggest that SCA events in which EO chemotaxis plays a role are likely to respond poorly to HU therapy. In

Table 1. Clinical profile of the patient

Parameter	**29-4-21**	**12-5-21**	**01-6-21**	**15-7-21**	**17-7-21**	**18-7-21**	**19-7-21**	**22-7-21**	**24-7-21**
Hemoglobin in g/dL	7.6	9	8.2	10	10.5	11	11	10.8	11.51
Total leucocyte count/µL	13.6	11.2	11.6	10.4	10.5	10	9.4	9	9.2
Differential count, %	N57, L17.8, E17	N37,L22 ,E29	N22,L23 ,**E38**	N59,L12 ,E19	N55, L12,E15	N65,L15 ,E14	N66,L19,E9	N67,L22,E6	N69,L22,E5
Platelets/µL $\times 10^3$	538	584	377	334	334	387	441	402	407
Blood Urea Nitrogen in mg/dL	12	15	16	14	15	15	15	17	15
Creatinine in mg/dL	0.60	0.73	0.74	0.64	0.8	0.6	0.7	0.74	0.73
Total /direct bilirubin in mg/dL	4.66/1.21	3.26/0.96	5.4/1.32	35.13/31.99	29.62/22.85	25.85	20.38	14.02	12.25/9.16
Aspartate transaminase (AST) (<40 U/L)	60	33	43	150	119	84	67	64	56
Alanine transaminase (ALT) (<40 U/L)	58	23	22	163	142	124	107	99	85
Alkaline phosphatase (SAP) (30-120 U/L)	108	102	90	214	208	212	209	200	191
gamma-glutamyltransferase, GGT(8-38 U/L)	62	68	60	328	306	240	241	167	159
Protein in g/dL	8.1	8	8	7.3	7.5	7.4	7.3	7.6	7.8
Albumin in g/dL	4.9	5	4.8	5.4	5.2	5.3	5.1	5.1	5.3
International normalized ratio(INR)	1.1	1.1	1	1.09	1.08	1.1	1	1	1

Table 2. Possible causes of Liver involvement in Sickle cell Anaemia

Pre-Hepatic Manifestations	**Haemolysis related-MC cause**	**Other pre-hepatic causes needs to ruled out**			
Hepatic Manifestations	Acute Sickle cell crisis Acute hepatic sequestration	Blood Transfusion related Viral infections	Iron overload	Intrahepatic cholestasis, Sickle cell cholangiopathy	DILI
Post Hepatic Manifestations	Gall stones diseases	Choledocolitiasis, cholangitis			

HU: hydroxyurea,

LFT: Liver function tests,

HRCT: High resolution computed tomography,

DILI: Drug induced Liver Injury,

RUCAM: Roussel Uclaf Causality Assessment Method,

SCD: Sickle cell diseases.

our case, patient's eosinophilia increased after HU intake, and worsened with continued intake, and therefore this is more likely a part of DILI rather than a part of SCA associated crises.

Hydroxyurea is commonly used in the treatment of sickle cell diseases and other oncological disorders. But DILI related to Hydroxyurea are rarely reported. One should rule out all the possible alternative causes before labelling a drug as a culprit of causation of liver injury and use of RUCAM score, obviates the need of liver biopsy to confirm DILI. Since patient recovered with the withdrawal of culprit drug, and re-challenged was positive, liver biopsy was not done.

HU related fatal hepatoxicity has been reported rarely especially with underlying hepatotropic viral infections like concurrent hepatitis B or C, or concurrent use of HIV medications like didansone, and stavudine combinations.[9] Moreover, Liver dysfunctions also reported with HU as a single agent for myeloproliferativedisorders.[10,11] Common clinical symptomatology were with fevers, lethargy, nausea, and vomiting. One trial of 36 patients using HU for the treatment of polycythaemiaVera observed hyperbilirubinemia in one patient but did not specify the degree to which the bilirubin was elevated or if HU was discontinued.[12,13,14] Available literature shows that liver dysfunction with HU, is often acute, starting within 1–4 weeks of initiating therapy and resolving in approximately 48 h after discontinuation of HU. Symptoms are similar in each of the case reports, with patients experiencing rigors, fever, abdominal pain, fatigue, and confusion; as is commonly seen in acute liver injury. The adverse event could be related to concurrent diseases, like HIV infections or dose related, can occur at doses ranging from 500 mg three times a week to 1000 mg daily and in patients with psoriasis, polycythaemiaVera, and essential thrombocytosis. All patients who were re-challenged in earlier studies had larger increases in total bilirubin and LFTs, as well as the quick onset of adverse effects, similar to our case. This observation suggests that HU should be permanently discontinued in patients experiencing elevations in LFTS and that no re-challenge is advisable. HU should be permanently discontinued in patients experiencing this toxicity.

Conclusion

HU is commonly used agent in oncology practice. HU related hepatotoxicity, although rare, but can be life threatening and therefore prompt recognition, high index of suspicion should be kept.

Author Contribution

Both authors contributed to this manuscript equally.

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References

1. Ahn H, Li CS, Wang W. Sickle cell hepatopathy: clinical presentation, treatment, and outcome in pediatric and adult patients. *Pediatr Blood Cancer*. 2005;45(2):184–190.
2. Shah R, Taborda C, Chawla S. Acute and chronic hepatobiliary manifestations of sickle cell disease: A review. *World J Gastrointest Pathophysiol*. 2017;8(3):108 –116.
3. Al Suleiman AM, Bu sobaih J. Acute fulminant cholestatic jaundice in sickle cell disease. *Ann Saudi Med*. 2006;26(2):138 –140.
4. Bandyopadhyay R, Bandyopadhyay SK, Dutta A. Sickle cell hepatopathy. *Indian J PatholMicrobiol*. 2008;51(2):284 –295.
5. Hallam MJ, Kolesar JM. Hydroxyurea induced acute elevations in liver function tests. *J Oncol Pharm Pract*. 2008;14(1):61 –63.
6. KwunLui S, Krasinskas A, Shah R. Orthotropic Liver Transplantation for Acute Intrahepatic Cholestasis in Sickle Cell Disease: Clinical and Histopathologic Features of a Rare Case. *Int J SurgPathol*. 2019;27(4):411 –417.
7. Canalli AA, Conran N, Fattori A. Increased adhesive properties of eosinophils in sickle cell disease. *ExpHematol*. 2004;32(8):728 –734.
8. FR Pallis, N Conran, KY Fertrin. Altered Functional Properties of Eosinophils in Sickle Cell Anemia and Effects of Hydroxyurea Therapy. *Blood*. 2010;116 (21): 2656.
9. Havlir DV, Gilbert PB, Bennett K. ACTG 5025 Study Group. Effects of treatment intensification with hydroxyurea in HIV –infected patients with virologic suppression. *AIDS*. 2001;27:1379–1388.
10. Sulkowski MS, Thomas DL, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA*. 2000;283:74–80.
11. Westerman DA, Schwarer A, Grigg AP. Hydroxyurea – induced fever and hepatitis. *Aust N Z J Med*. 1998;28: 657–659.
12. Heddle R, Calvert AF. Hydroxyurea induced hepatitis. *Med J Aust.* 1980;1:121.
13. Sharon R, Tatarsky I, Ben Arieh Y. Treatment of Polycythemia Vera with Hydroxyurea. *Cancer*. 1986;57:718–720.
14. Malec J, Szczepanska I, Grabarczyk M. Hydroxyurea –induced toxic side –effects in animals and an attempt at reducing them with vitamins E and C. *Neoplasma*. 1989;36:427–435.