Case Report

Hemoglobin H Disease: A rare case report and its diagnostic challenge

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Abstract

Thalassemia the most common monogenic gene disorder in the world is especially frequent in Mediterranean countries. Hemoglobin H (Hb H) disease is a special variant of α-thalassemia presenting as microcytic hypochromic anemia. The clinical phenotypes of most individuals remain unnoticed unless there occurs an acute hemolytic crisis and they are most often under-diagnosed or misdiagnosed as iron deficiency anemia. Here we report a case of 34 year old pregnant women who presented with pallor and mild splenomegaly. Complete blood count (CBC) showed decrease in Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC) and increase in Red Cell Distribution Width (RDW) and reticulocyte percent. Peripheral smear showed microcytic hypochromic Red Blood Corpuscles (RBCs) with severe anisopoikilocytosis. Supravital staining of peripheral blood showed Hb H inclusions in RBCs. The increase in reticulocyte percent here is due to mature RBC's having Hb H inclusions that are misinterpreted as reticulocytes by automated cell counters. Hence, in a background of variable clinical presentation of this disease, we consider this case to highlight the importance of simple peripheral smear examination and supravital staining of peripheral blood in the diagnosis of Hb H disease which are often misdiagnosed as iron deficiency anemia by seeing CBC results. It is also important to emphasize the importance of early diagnosis of these cases to facilitate implementation of proper preventive health care measure, ensure fetal well being and prompt treatment of potentially serious hemolytic crisis that can occur during pregnancy.

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Introduction

Hb H disease is a special variant of α-thalassemia that is more prevalent in South East Asia, Middle East and Mediterranean and in Indian subcontinentbecause of high carrier frequency of ($--^{SEA}$) type of α-thalassemia deletion gene [1]. The clinical phenotypes of most individual with Hb H disease are very mild and may not be noticed during his/her entire life unless a routine full blood count is done or when there is an acute hemolytic crisis in conditions like infections, pregnancy like in our case where anemia is not improved even after iron/folic acid therapy. It is virtually important to carry out prospective and in depth studies of pregnancy in women with Hb H disease to define the risk and criteria for treatment. Another important issue is related to testing the women's partner and genetic counselling [2].

Case Report

A 34 year-old pregnant women came for her general checkup to our hospital. She had a previous history of cesarean section and 3 units of blood transfusion during her last pregnancy. During the present pregnancy she presented with pallor and mild splenomegaly. Her Hb started decreasing in-spite of taking regular oral iron/folic acid therapy. She has been treated with repeated blood transfusions. In between her pregnancies she was absolutely asymptomatic.There was no family history and her first child was apparently normal.Aroutine complete blood analysis was done using automated cell counterand report as follows: Hb- 8.4gm%, MCV-57.5fl, MCH-17.8pg, MCHC-31.0g/dl, Total RBC count -$4.71\times10^{9/}$cu.mm, RDW-28.2%. Total Leucocyte Count -11,700/cu.mm and platelet count-1.6lacs/cu.mm, Reticulocyte count-6%.Peripheral smear showed microcytic hypochromic RBC's with severe anisopoikilocytosis. Good number ofteardropcells, elongated cells and target cells were seen (Figure-1). Few cells show basophilic stippling.WBC showed neutrophilia with toxic granules. Supravital staining with 1% brilliant cresyl blue of peripheral blood showed Hb H inclusions (Figure-2). Hb electrophoresis by agarose gel showed thick band in "A" region. High Pressure Liquid Chromatography (HPLC) showed presence of Hb H. With these findings a diagnosis of α- thalassemia (Hb H disease) was made.

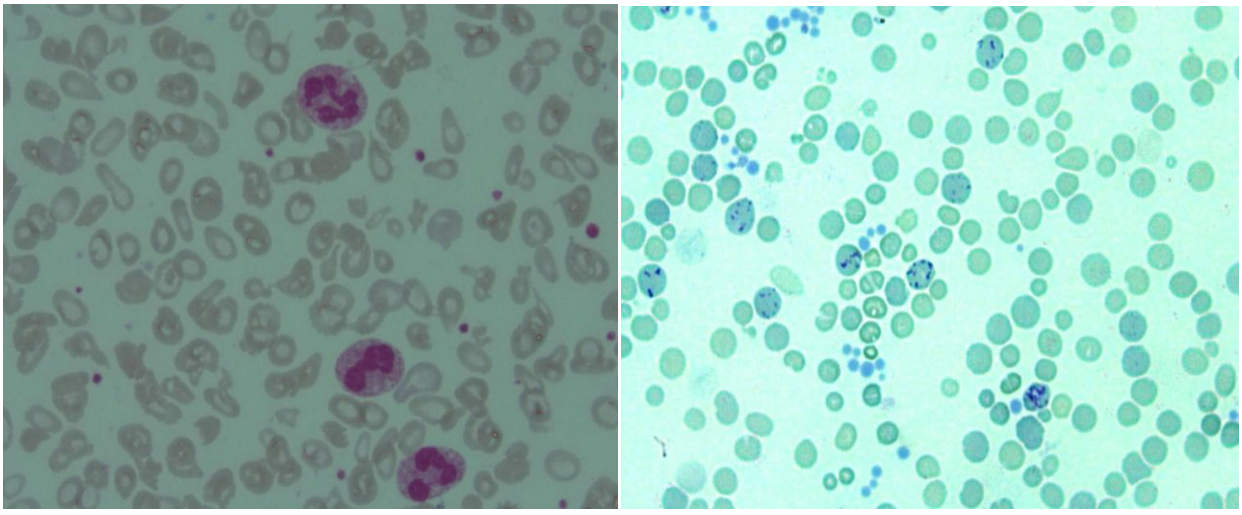

FIGURE 1: Microcytic and hypochromic RBCs with anisopoikilocytes- tear drop cells, target cells.(Leishman Stain, 400X)

FIGURE 2: Cells showing golf like inclusion bodies in new methylene blue stain (x400X).

Discussion

Thalassemia is perhaps the most common single-gene disorder in the world. More than 50% of the population appears to have a clinically silent form of α-thalassemia. HbH disease is recognized with increasing frequency in the eastern oasis of Saudi Arabia[3]. Around 300,000-400,000 severely affected infants are born every year, more than 95%, of who are in Asia, India, or the Middle East. Hb H disease results from the presence of only one functional α gene, usually as a consequence of the compound heterozygous state for α^0-thalassemia/α^+-thalassemia (–/-α or –/$\alpha^T\alpha$). It occurs due to deletion or non-deletion mutations in α-gene on chromosome 16. The disease presents with different phenotype ranging from asymptomatic to need for periodic transfusions, and fatal fetal hydropsfetalis in utero [4]. The severity is high in case of non-deletion mutation, constant spring mutation and if α_2 gene is affected [5]. When the level of α globulin gene synthesis falls below 70% of normal in adult life the excess βglobulin chains form tetramers of Hb H in the cell.The typical inclusion-body cells have a golf-ball like appearance with stippling regularly distributed over a blue stained background.

HbH has a high affinity for oxygen. These Hb H inclusions bind with the band 3 protein in RBC cell membrane and causes damage mostlyto mature red cells and a lesser extent to erythroid precursors, leading mainly to hemolysis and minimally to ineffective erythropoiesis. Certain conditions like infections, pregnancy and intake of certain oxidant drugs increases the Hb H inclusions leading to acute hemolytic crisis and precipitous drop in Hb. All affected individuals have a variable degree of anemia, decreased MCV and MCH and normal or slightly reduced level of Hb A_2.

The amount of Hb H may be variable ranging from 1-40%. This HbH (fastest Hb) may escape from detection because of its high instability. Molecular analysis is required to confirm the hematological observation.

The important differential diagnosis that to be considered is iron deficiency anemia the most common anemia in pregnancy in India which also presents with decreased MCV, MCH, MCHC and increase in RDW and reticulocyte percent when on treatment. Since the Hb of the patient drops down when she was on iron therapy, the increase in reticulocyte percent couldnot is due to iron therapy. It is due to mature RBCs containing Hb H inclusions that are regarded as reticulocytes by cell counters. This entitles the importance of detailed peripheral smear examination along with a supra-vital staining showing Hb H inclusions in the diagnosis of Hb H disease and provides a way for other investigations like genetic studies for further evaluation. If diagnosed early it prevents from other unnecessary tests and false treatment to the patient with iron therapy. Other conditions where we could find Hb H inclusions are erythroleukemia and myelodysplasia. But the clinical condition and investigations done does not correlate with the above conditions.

It is also important to identify couples at the earliest who are at risk of conceiving fetus with Hb H disease. When one parent carries α^{o} thalassaemia (--/αα) and the other carries an α^{+} thalassaemia (-α/αα) the risk of their offspring having HbH disease is 1:4 (25%). If the carrier of α^{+} thalassaemia is a homozygote clearly the risk of HbH disease is 1:2 (50%) [6]. Therefore, in these cases prenatal diagnosis should be done. It can be made by fetal DNA analysis at the earliest by 9-12 weeks by Chorionic Villous Sampling. DNA based diagnosis are highly accurate and specific.

HbH disease places fetuses at significant risk for growth restriction, preterm birth, and low birth weight, resulting in increased perinatal mortality [7]. Since both pregnancy and thalassemia are associated with a higher risk of thrombosis due to a hypercoagulable state, pregnant women with HbH disease will theoretically be at higher risk for thromboembolism [8]. Common obstetric complications, such pre-eclampsia, antepartum hemorrhage, and postpartum hemorrhage have been noted in some studies.

Conclusion

HbH disease is an under-diagnosed entity in the Indian subcontinent. We feel that a careful evaluation for Hb H inclusions on reticulocyte preparation would help in diagnosing these cases. The early diagnosis of these cases will also facilitate implementation of proper preventive health care measure, ensure fetal well being and prompt treatment of potentially serious hemolytic crisis and infection and also to heighten the awareness of other devastating α and β thalassemia syndromes in the community.

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Competing Interests

None declared.

References

1. Chui DHK, Waye JS. Hydropsfetalis caused by α-thalassemia: an emerging health care problem. Blood. 1998; 91:2213-2222.
2. David H. K. Chui, SuthatFucharoen, and Vivian Chan. Hb H disease: not necessarily a benign disorder blood, 2003 volume 101, number 3.
3. Munchi N, De Silva V, While IM. The frequencies of HbS α and β-thalassemia in Saudi Arabia Preliminary national values. Saudi Med J 1989; 10:62–65.
4. Mirabile E, Samperi P, Di Cataldo A, Poli A, La Spina M, Schilirb G. Phenotype-genotype correlation in Sicilian patients with Hb H. Eur J Haematol. 2000; 65:306-309.
5. Fucharoen S, Winichagoon P, Pootrakul P, et al. Differences between two types of Hb H disease, alpha-thalassemia 1/alpha-thalassemia 2 and alpha-thalassemia 1/Hb constant spring. Birth Defects Orig Artic Ser 1987;23: 309–315.
6. Cornelis L Harteveld, Douglas R Higgs. α- thalassemia Harteveld and Higgs Orphanet Journal of Rare Diseases 2010, **5**:13.
7. Theera Tongsong, Kasemsri Srisupundit, Suchaya Luewan. Outcomes of pregnancies affected by hemoglobin H disease International Journal of Gynecology and Obstretics 104 (2009) 206-208.
8. Taher A, Isma'eel H, Mehio G, Bignamini D, Kattamis A, Rachmilewitz EA, et al. Prevalence of thromboembolic events among 8,860 patients with thalassaemiamajor and intermedia in the Mediterranean area and Iran. ThrombHaemost 2006;96(4):488–91.